US009284283B2

(12) **United States Patent**
Taylor et al.

(10) **Patent No.: US 9,284,283 B2**
(45) **Date of Patent: Mar. 15, 2016**

(54) **MACROCYCLIC COMPOUNDS FOR MODULATING IL-17**

(71) Applicant: **ENSEMBLE THERAPEUTICS CORPORATION**, Cambridge, MA (US)

(72) Inventors: **Michael Taylor**, Lexington, MA (US); **Nicholas K. Terrett**, Sherborn, MA (US); **William H. Connors**, Lynnfield, MA (US); **Cheri Snedeker**, Nashua, NH (US); **Kelley C. Shortsleeves**, Maynard, MA (US); **Benjamin A. Seigal**, Newton, MA (US); **Stephen P. Hale**, Belmont, MA (US); **Timothy F. Briggs**, Cambridge, MA (US); **Frank G. Favaloro, Jr.**, North Attleboro, MA (US); **Tyler J. Cipriani**, North Stonington, CT (US); **Dingxue Yan**, South Grafton, MA (US); **Sethu L. Alexander**, Westford, MA (US); **Atli Thorarensen**, Stow, MA (US); **Li Xing**, Lexington, MA (US)

(73) Assignee: **Ensemble Therapeutics Corporation**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/376,247**

(22) PCT Filed: **Feb. 1, 2013**

(86) PCT No.: **PCT/US2013/024386**
§ 371 (c)(1),
(2) Date: **Aug. 1, 2014**

(87) PCT Pub. No.: **WO2013/116682**
PCT Pub. Date: **Aug. 8, 2013**

(65) **Prior Publication Data**

US 2015/0005319 A1 Jan. 1, 2015

Related U.S. Application Data

(60) Provisional application No. 61/593,993, filed on Feb. 2, 2012, provisional application No. 61/725,878, filed on Nov. 13, 2012.

(51) **Int. Cl.**

C07D 257/10	(2006.01)
C07D 273/00	(2006.01)
C07D 401/12	(2006.01)
C07D 409/14	(2006.01)
C07D 413/12	(2006.01)
C07D 409/12	(2006.01)
C07D 405/12	(2006.01)
C07D 257/02	(2006.01)
C07D 403/12	(2006.01)
C07D 417/12	(2006.01)
A61K 31/4965	(2006.01)
A61K 31/33	(2006.01)
A61K 31/44	(2006.01)
A61K 31/445	(2006.01)
A61K 31/425	(2006.01)

(Continued)

(52) **U.S. Cl.**
CPC ***C07D 257/10*** (2013.01); ***A61K 31/366*** (2013.01); ***A61K 31/42*** (2013.01); ***A61K 38/00*** (2013.01); ***C07D 255/02*** (2013.01); ***C07D 257/02*** (2013.01); ***C07D 273/00*** (2013.01); ***C07D 401/12*** (2013.01); ***C07D 403/12*** (2013.01); ***C07D 405/12*** (2013.01); ***C07D 409/12*** (2013.01); ***C07D 409/14*** (2013.01); ***C07D 413/12*** (2013.01); ***C07D 417/12*** (2013.01)

(58) **Field of Classification Search**
USPC 514/255.05, 183, 256, 278, 326, 365, 514/374, 444, 451; 540/453, 460, 461
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,952,320	A	9/1999	Davidsen et al.
6,100,235	A	8/2000	Yao et al.

(Continued)

FOREIGN PATENT DOCUMENTS

WO	WO-0168705	9/2001
WO	WO-0208285	1/2002

(Continued)

OTHER PUBLICATIONS

Cancer [online], [retrieved on Jul. 6, 2007] Retrieved from the Internet, URL: http://www.nlm.nih.gov/medlineplus/cancer.html.*

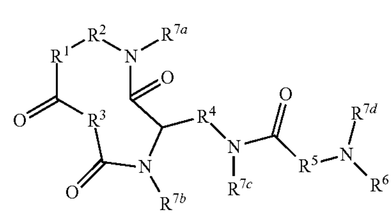
(Continued)

Primary Examiner — Kristin Vajda
(74) *Attorney, Agent, or Firm* — Goodwin Procter LLP

(57) **ABSTRACT**

The invention relates generally to macrocyclic compounds of formula I and their therapeutic use. More particularly, the invention relates to macrocyclic compounds that modulate the activity of IL-17 and/or are useful in the treatment of medical conditions, such as inflammatory diseases and other IL-17-associated disorders.

(I)



16 Claims, 284 Drawing Sheets

(51) **Int. Cl.**

A61K 31/42	(2006.01)
A61K 31/38	(2006.01)
A61K 31/35	(2006.01)
A61K 38/00	(2006.01)
A61K 31/366	(2006.01)
C07D 255/02	(2006.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,427,402	B2	9/2008	Kastelein et al.
7,501,247	B2	3/2009	Kastelein et al.
7,510,709	B2	3/2009	Gurney
7,611,857	B2	11/2009	Medlock et al.
7,622,116	B2	11/2009	Kuestner et al.
7,740,848	B2	6/2010	Kastelein et al.
7,776,540	B2	8/2010	Kastelein et al.
7,790,163	B2	9/2010	Jaspers et al.
7,790,862	B2	9/2010	Lewis et al.
7,807,155	B2	10/2010	Di Padova et al.
7,910,540	B2	3/2011	Levin et al.
7,910,703	B2	3/2011	Lewis et al.
8,119,131	B2	2/2012	Di Padova et al.
8,178,095	B2	5/2012	Kastelein et al.
8,183,040	B2	5/2012	Manel et al.
8,268,773	B2	9/2012	Presnell et al.
8,287,869	B2	10/2012	Gurney
8,338,565	B2	12/2012	Lee et al.
2002/0037524	A1	3/2002	Medlock et al.
2003/0124092	A1	7/2003	Medlock et al.
2004/0136992	A1	7/2004	Burton et al.
2005/0287593	A1	12/2005	Kastelein et al.
2006/0270003	A1	11/2006	Arnott et al.
2007/0123459	A1	5/2007	Medlock et al.
2007/0154487	A1	7/2007	Littman et al.
2007/0160576	A1	7/2007	Arnott et al.
2007/0212362	A1	9/2007	Filvaroff
2007/0238658	A1	10/2007	Levin et al.
2007/0249533	A1	10/2007	Levin et al.
2008/0031882	A1	2/2008	Liang et al.
2008/0199460	A1	8/2008	Cua et al.
2008/0241130	A1	10/2008	Wright et al.
2008/0248025	A1	10/2008	Roark et al.
2008/0269467	A1	10/2008	Allan et al.
2009/0274703	A1	11/2009	Mohler
2009/0300776	A1	12/2009	Lecron et al.
2010/0021456	A1	1/2010	Miossec et al.
2010/0111950	A1	5/2010	Cua et al.
2010/0111954	A1	5/2010	Cua et al.
2010/0239590	A1	9/2010	Bowman et al.
2010/0247547	A1	9/2010	Dong et al.
2011/0033451	A1	2/2011	Carreno et al.
2011/0091378	A1	4/2011	Dudas et al.
2011/0104236	A1	5/2011	Dana et al.
2011/0142831	A1	6/2011	Cua et al.
2011/0144303	A1	6/2011	Nash et al.
2011/0152173	A1	6/2011	Lofquist et al.
2011/0159589	A1	6/2011	Lewis et al.
2011/0177578	A1	7/2011	Nakamura et al.
2011/0212099	A1	9/2011	Liang et al.
2011/0212100	A1	9/2011	Keller et al.
2011/0236390	A1	9/2011	Almagro et al.
2011/0256126	A1	10/2011	Arnott et al.
2011/0263479	A1	10/2011	Jacobsen et al.
2011/0289608	A1	11/2011	Schnell et al.
2011/0293629	A1	12/2011	Bastid et al.
2011/0311519	A1	12/2011	Teitelbaum et al.
2011/0318301	A1	12/2011	Arnott et al.
2012/0009190	A1	1/2012	Gaffen et al.
2012/0107325	A1	5/2012	Di Padova et al.
2012/0142755	A1	6/2012	Lecron et al.
2012/0196861	A1	8/2012	Leban et al.
2012/0196862	A1	8/2012	Leban et al.
2012/0244543	A1	9/2012	Manel et al.
2012/0252896	A1	10/2012	Ernst et al.
2012/0263729	A1	10/2012	Burton et al.
2012/0276105	A1	11/2012	Kastelein et al.
2014/0309265	A1	10/2014	Seigal et al.

FOREIGN PATENT DOCUMENTS

WO	WO-03055980		7/2003
WO	WO-03057722	A2	7/2003
WO	WO-2004019866	A2	3/2004
WO	WO-2004042009	A2	5/2004
WO	WO-2005010044	A2	2/2005
WO	WO-2005098435	A2	10/2005
WO	WO-2005108616	A1	11/2005
WO	WO-2005123778	A2	12/2005
WO	WO-2006013107	A1	2/2006
WO	WO-2006063864	A2	6/2006
WO	WO-2006088833	A2	8/2006
WO	WO-2007027761	A2	3/2007
WO	WO-2007038703	A2	4/2007
WO	WO-2007147019	A2	12/2007
WO	WO-2007149814	A1	12/2007
WO	WO-2008039553	A1	4/2008
WO	WO-2008067223	A2	6/2008
WO	WO-2008104000	A2	8/2008
WO	WO-2008118792	A2	10/2008
WO	WO-2008121865	A1	10/2008
WO	WO-2008131315	A2	10/2008
WO	WO-2008134659	A2	11/2008
WO	WO-2008150885	A1	12/2008
WO	WO-2008156865	A2	12/2008
WO	WO-2009015063	A2	1/2009
WO	WO-2009023267	A2	2/2009
WO	WO-2009047523	A1	4/2009
WO	WO-2009082624	A2	7/2009
WO	WO-2009089036	A2	7/2009
WO	WO-2010003108	A2	1/2010
WO	WO-2010022249	A2	2/2010
WO	WO-2010062858	A1	6/2010
WO	WO-2010144344	A2	12/2010
WO	WO-2011053763	A2	5/2011
WO	WO-2011061667	A1	5/2011
WO	WO-2011062628	A1	5/2011
WO	WO-2011100567	A1	8/2011
WO	WO-2011141823	A2	11/2011
WO	WO-2011143608	A1	11/2011
WO	WO-2011163452	A2	12/2011
WO	WO-2012059598	A2	5/2012
WO	WO-2012082573	A1	6/2012
WO	WO-2012101261	A1	8/2012
WO	WO-2012101263	A1	8/2012
WO	WO-2013016220	A1	1/2013
WO	WO-2013071027	A1	5/2013
WO	WO-2013071035	A1	5/2013
WO	WO-2013071039	A1	5/2013

OTHER PUBLICATIONS

Lala et al., Role of nitric oxide in tumor progression: Lessons from experimental tumors, Cancer and Metastasis Reviews (1998), 17, 91-106.*

Golub et al., Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring, Science (1999), vol. 286, 531-537.*

Appel et al. (2011) "Analysis of IL-17+ cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response," Arthritis Research and Therapy 13:R95.

Bednarek et al. (2001) "Selective, high affinity peptide antagonists of alpha-melanotropin action at human melanocortin receptor 4: Their synthesis and biological evaluation in vitro," Journal of Medicinal Chemistry 44(22): 3665-3672.

Dudler et al. (2000) "Effect of interleukin 17 on proteoglycan degradation in murine knee joints," Ann Rheum Dis 59:529-32.

Flygare et al. (2010) "Small-molecule pan-IAP antagonists: a patent review," Expert Opinion on Therapeutic Patents 20(2): 251-267.

Gaffen (2004) "Biology of recently discovered cytokines: Interleukin-17—a unique inflammatory cytokine with roles in bone biology and arthritis," Arthritis Research & Therapy 6: 240-247.

(56) **References Cited**

OTHER PUBLICATIONS

Gaffen (2009) "Structure and signalling in the IL-17 receptor family," Nature Rev Immunol, 9: 556-567.
Giolitti et al. (2002) "Monocyclic human tachykinin NK-2 receptor antagonists as evolution of a potent bicyclic antagonist: QSAR and site-directed mutagenesis studies," Journal of Medicinal Chemistry 45(16): 3418-3429.
International Search Report and Written Opinion for International Patent Application No. PCT/US2009/054487, mailed on Feb. 15, 2010 (18 pages).
International Search Report and Written Opinion for International Patent Application No. PCT/US2012/064332, mailed on Feb. 21, 2013 (7 pages).
International Search Report and Written Opinion for International Patent Application No. PCT/US2012/064342, mailed on Jan. 24, 2013 (8 pages).
International Search Report and Written Opinion for International Patent Application No. PCT/US2012/064349, mailed on Jan. 30, 2013 (10 pages).
Ji et al. (2010) "Th17 cells: positive or negative role in tumor?" Cancer Immunol Immunother 59: 979-987.
Lubberts et al. (2001) "IL-1 Independent Role of IL-17 in Synovial Inflammation and Joint Destruction During Collagen-Induced Arthritis," J Immunol 167:1004-1013.
Matusevicius et al. (1999) "Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis," Multiple Sclerosis 5:101-104.
McInnes et al. (2011) "Anti-Interleukin 17A Monoclonal Antibody Secukinumab Reduces Signs and Symptoms of Psoriatic Arthritis in a 24-Week Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial. [abstract]," Arthritis & Rheumatism 63: Suppl.10:779.
Miyazaki et al. (2004) "Design and synthesis of nobel type somatostatin analogs with antiproliferative activities on A431 tumor cells," Tetrahedrin Letters 45(33): 6323-6327.
Nakae et al. (2003) "Suppression of Immune Induction of Collagen-Induced Arthritis in IL-17-Deficient Mice," J Immunol 171:6173-6177.
Nikolovska-Coleska et al. (2008) "Interaction of a Cyclic. Bivalent Smac Mimetic with the X-Linked Inhibitor of Apoptosis Protein," Biochemistry 47(37): 9811-9824.
Pedersen et al. (2011) "1.2.3-Triazoles in Peptidomimetic Chemistry," European Journal of Organic Chemistry 13: 2399-2411.
Prabhala et al. (2010) "Elevated IL-17 produced by Th17 cells promotes myeloma cell growth and inhibits immune function in multiple myeloma," Blood 115(26): 5385-5392.
Rothe et al. (1976) "Makrocyclische Peptide in Anionischen Polymerisaten Von Aminosaeure-N-Carbonsaeureanhydriden," Angewandte Chemie 88(10): 338-339.
Schwyzer et al. (1956) "Synthesen zyklischer Polypeptide. c-Tetraglycyl and c-Hexaglycyl. Uber aktivierte Ester VII," Helvetica Chimica Acta 39(3): 872-883.
Sheh et al. (1985) "Cyclization Studies of Tetrapeptide Homologs," Tetrahedron Letters 26(47): 5755-5758.
Shlezinger et al. (2011) "Apoptosis-like programmed cell death in the grey mould fungus Botrytis cinerea: genes and their role in pathogenicity," Biochemical Society Transactions 39(5): 1493-1498.
Smolewski et al. (2011) "Inhibitors of apoptosis proteins (IAPs) as potential molecular targets for therapy of hematological malignancies," Current Molecular Medicine 11(8): 633-49.
Spriggs et al. (1997) "Interleukin-17 and Its Receptor," J Clin Immunol, 17: 366-369.
STN Search Transcript Registry/Caplus Databases (2013) 162 pages.
Sun et al. (2010) "Cyclopeptide Smac mimetics as antagonists of IAP proteins," Bioorganic & Medicinal Chemistry Letters 20(10): 3043-3046.
Zhang et al. (2009) "Increased intratumoral IL-17-producing cells correlate with poor survival in hepatocellular carcinoma patients" J Hepatology 50: 980-89.

* cited by examiner

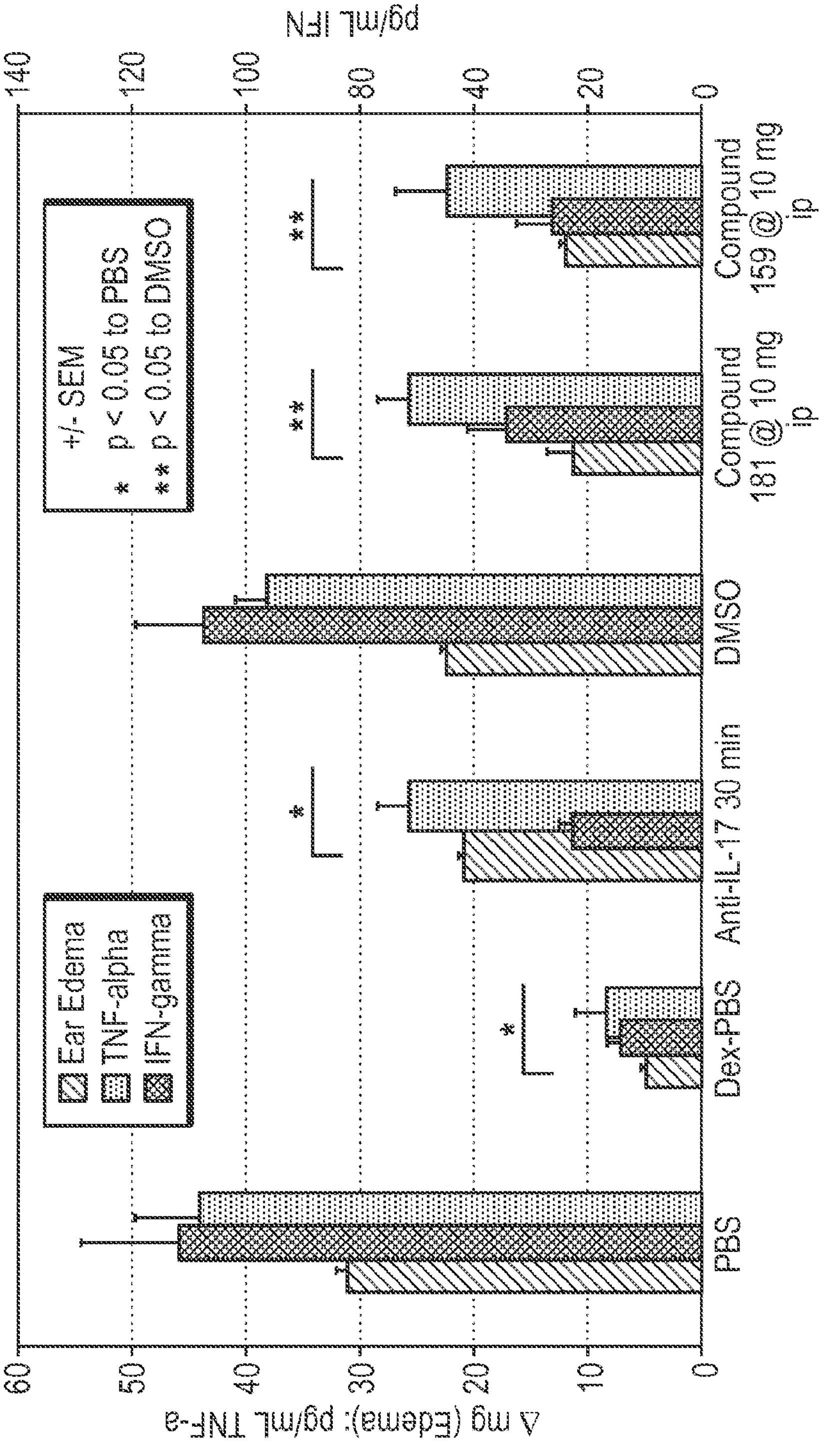

Ear Edema
TNF-alpha
IFN-gamma
+/- SEM
* p < 0.05 to PBS
** p < 0.05 to DMSO
Δ mg (Edema): pg/mL TNF-a
pg/mL IFN
0
10
20
30
40
50
60
0
20
40
60
80
100
120
140
PBS
Dex-PBS
Anti-IL-17 30 min
DMSO
Compound 181 @ 10 mg ip
Compound 159 @ 10 mg ip
*
*
**
**

FIG. 1

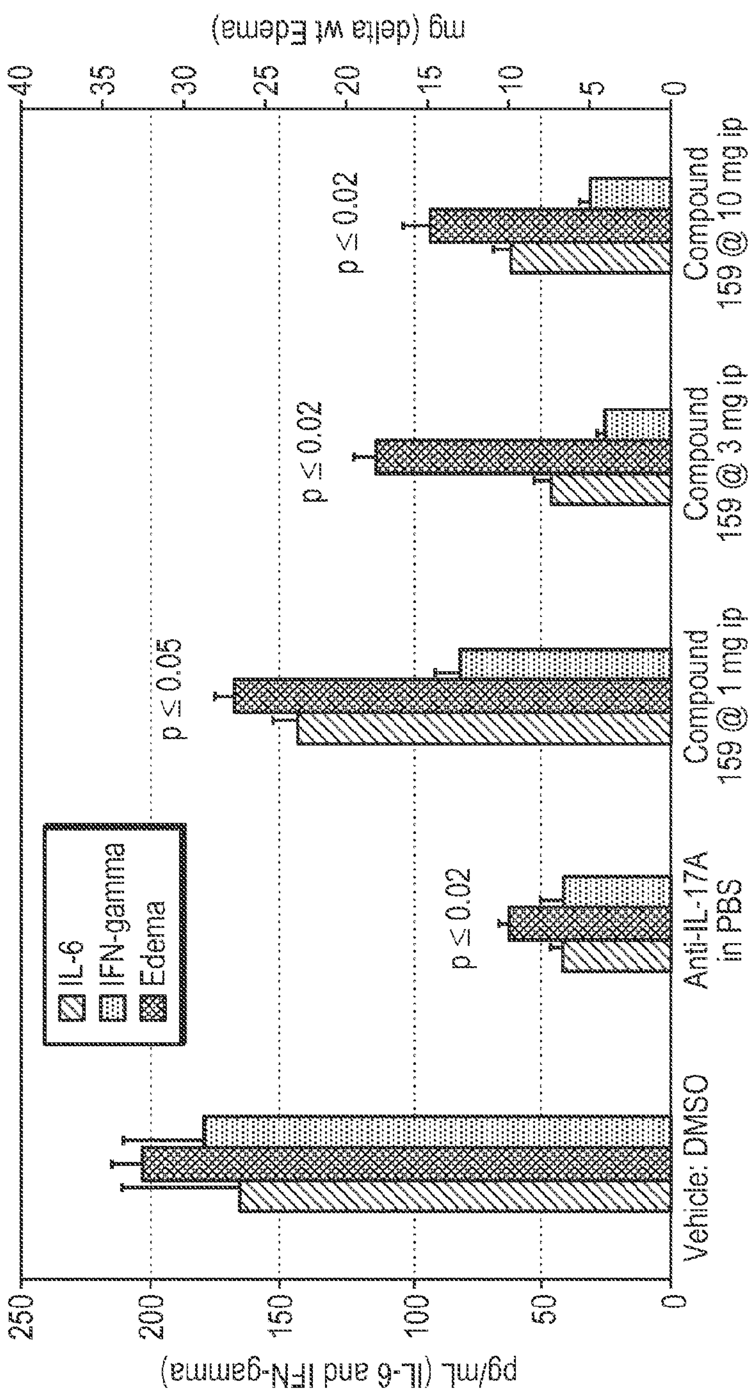
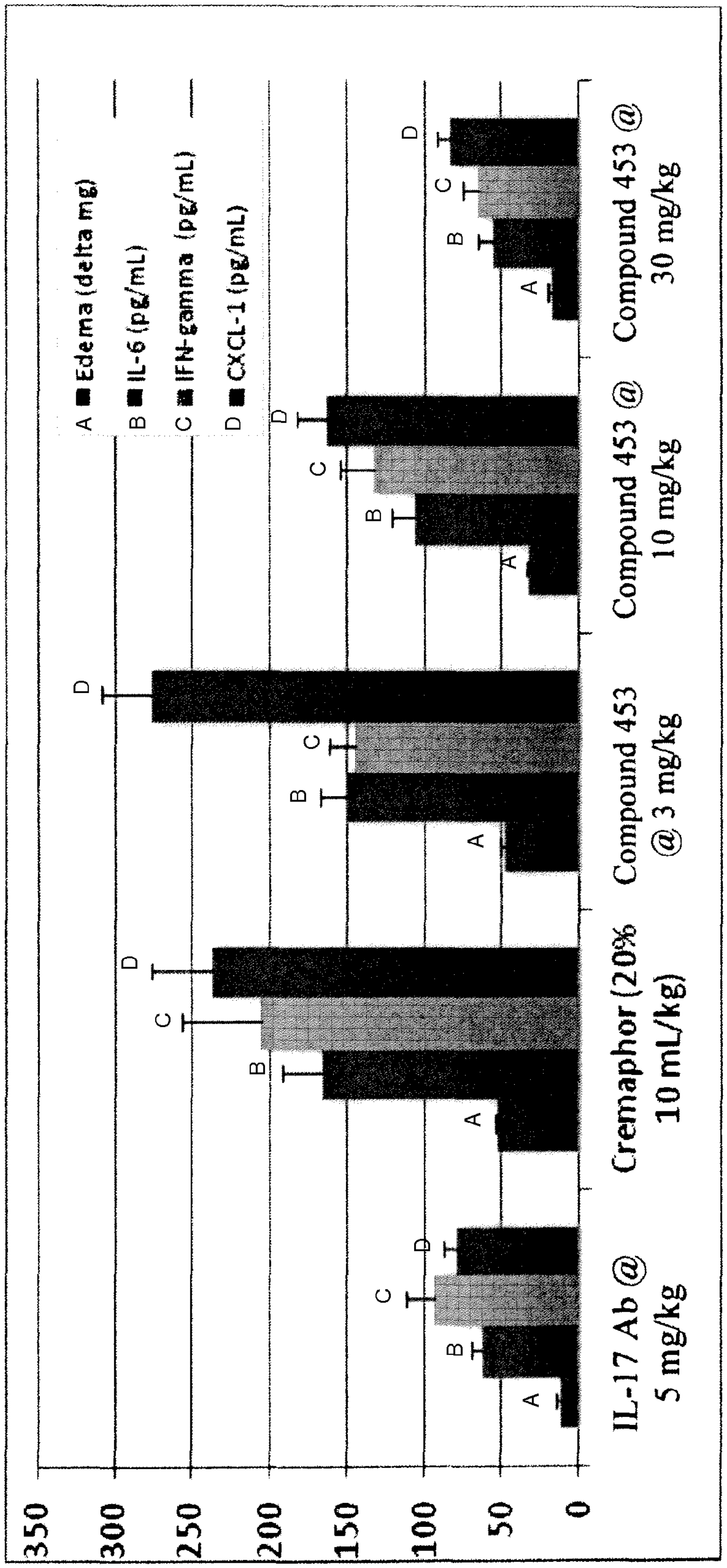

pg/mL (IL-6 and IFN-gamma)
mg (delta wt Edema)
250
200
150
100
50
0
40
35
30
25
20
15
10
5
IL-6
IFN-gamma
Edema
p ≤ 0.02
p ≤ 0.05
p ≤ 0.02
p ≤ 0.02
Vehicle: DMSO
Anti-IL-17A in PBS
Compound 159 @ 1 mg ip
Compound 159 @ 3 mg ip
Compound 159 @ 10 mg ip

FIG. 2

FIG. 3



A ■ Edema (delta mg)
B ■ IL-6 (pg/mL)
C ■ IFN-gamma (pg/mL)
D ■ CXCL-1 (pg/mL)
0
50
100
150
200
250
300
350
IL-17 Ab @ 5 mg/kg
Cremaphor (20% 10 mL/kg)
Compound 453 @ 3 mg/kg
Compound 453 @ 10 mg/kg
Compound 453 @ 30 mg/kg

FIG. 4

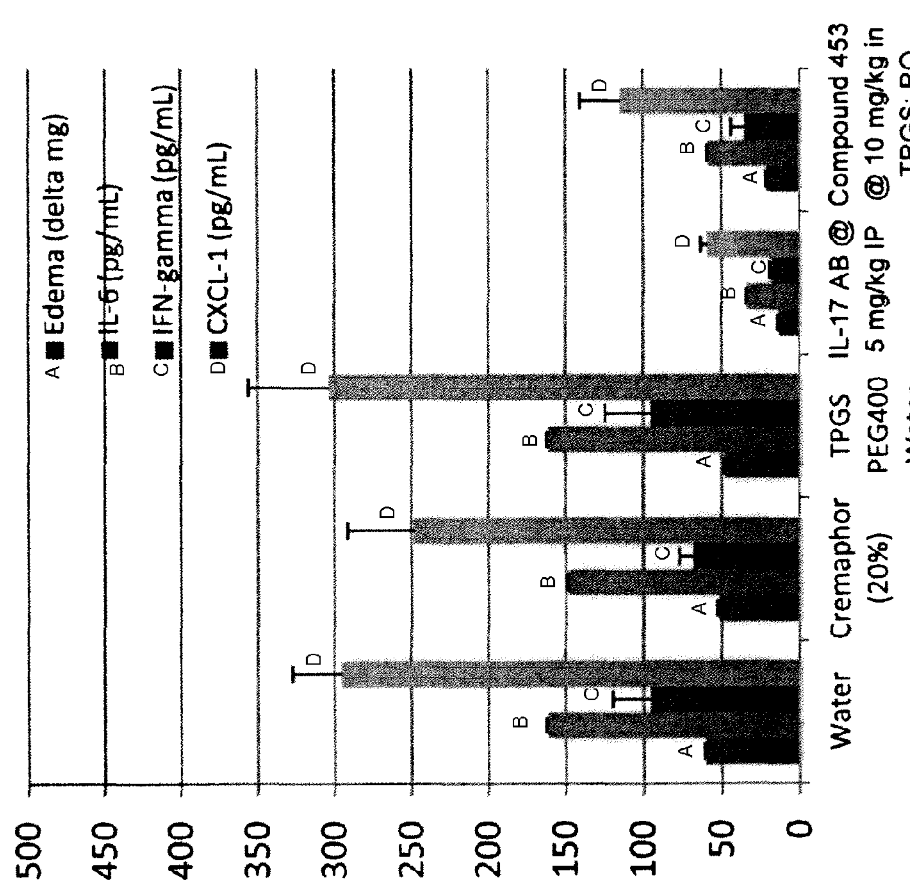
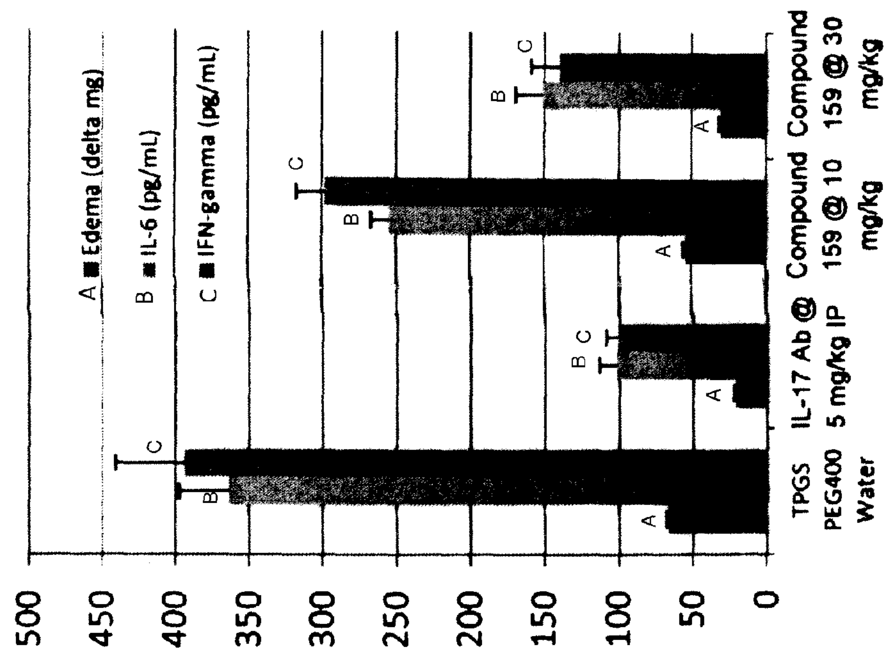

A Edema (delta mg)
B IL-6 (pg/mL)
C IFN-gamma (pg/mL)
D CXCL-1 (pg/mL)
500
450
400
350
300
250
200
150
100
50
0
Water
Cremaphor (20%)
TPGS PEG400 Water
IL-17 AB @ 5 mg/kg IP
Compound 453 @ 10 mg/kg in TPGS; PO

FIG. 5


A ■ Edema (delta mg)
B ■ IL-6 (pg/mL)
C ■ IFN-gamma (pg/mL)
500
450
400
350
300
250
200
150
100
50
0
TPGS PEG400 Water
IL-17 Ab @ 5 mg/kg IP
Compound 159 @ 10 mg/kg
Compound 159 @ 30 mg/kg
A
B
C

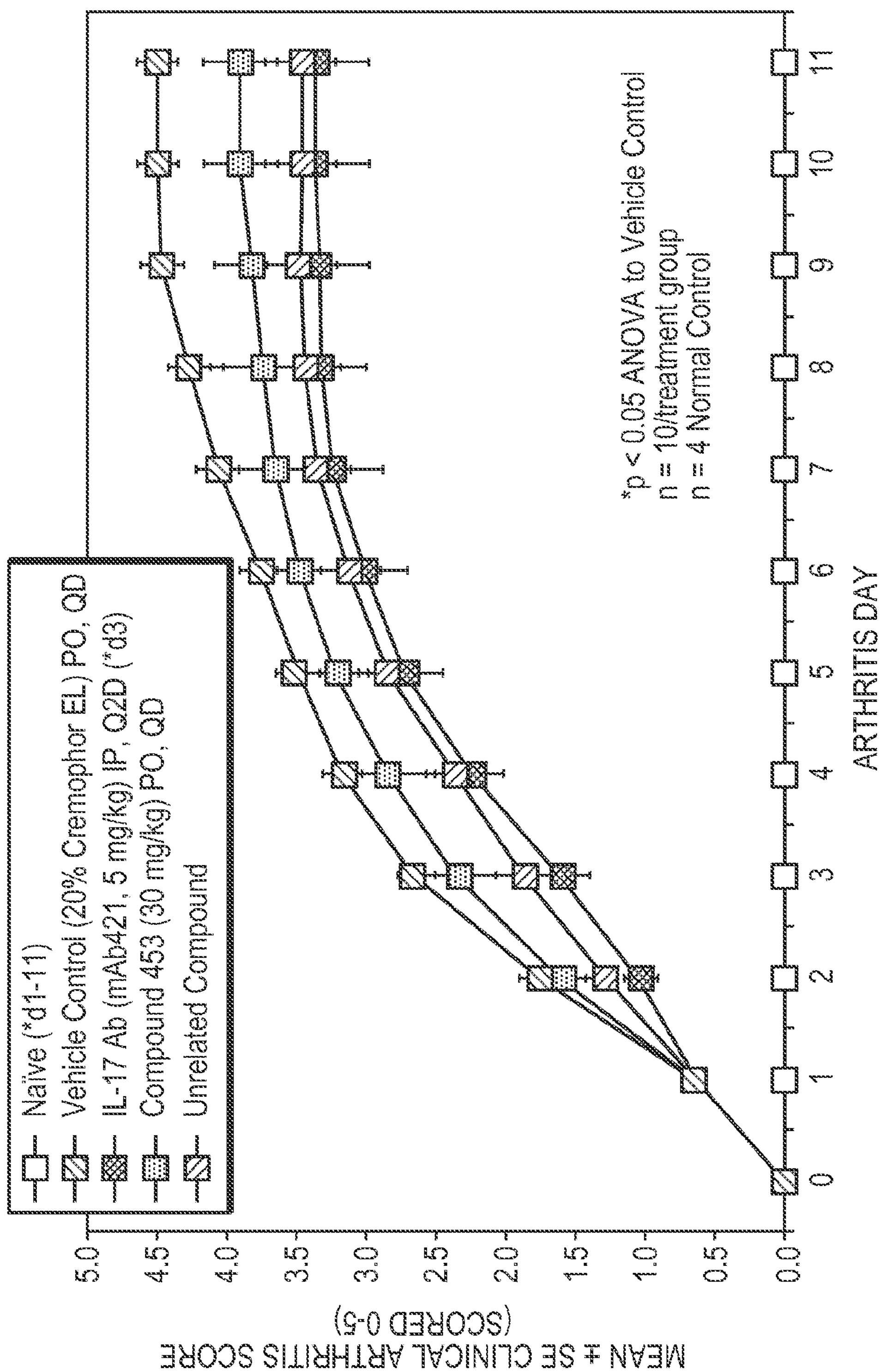

Naïve (*d1-11)
Vehicle Control (20% Cremophor EL) PO, QD
IL-17 Ab (mAb421, 5 mg/kg) IP, Q2D (*d3)
Compound 453 (30 mg/kg) PO, QD
Unrelated Compound
*p < 0.05 ANOVA to Vehicle Control
n = 10/treatment group
n = 4 Normal Control
MEAN ± SE CLINICAL ARTHRITIS SCORE (SCORED 0-5)
ARTHRITIS DAY
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
0
1
2
3
4
5
6
7
8
9
10
11

FIG. 6

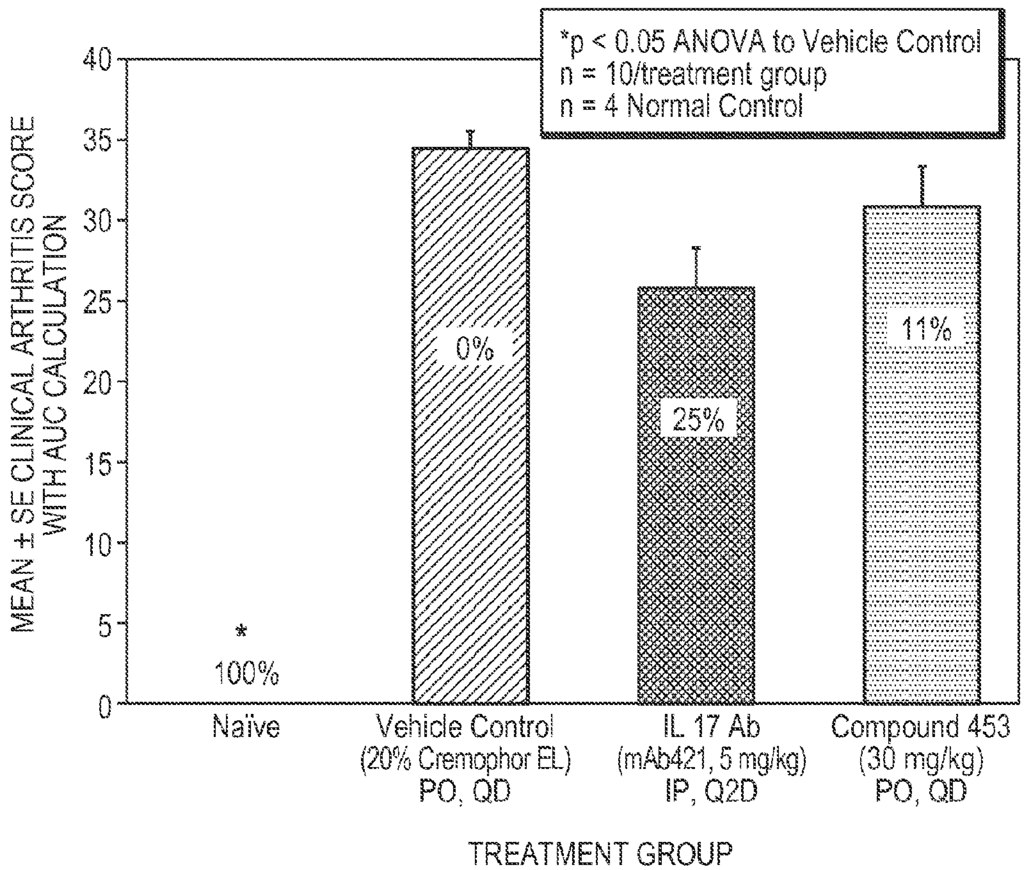
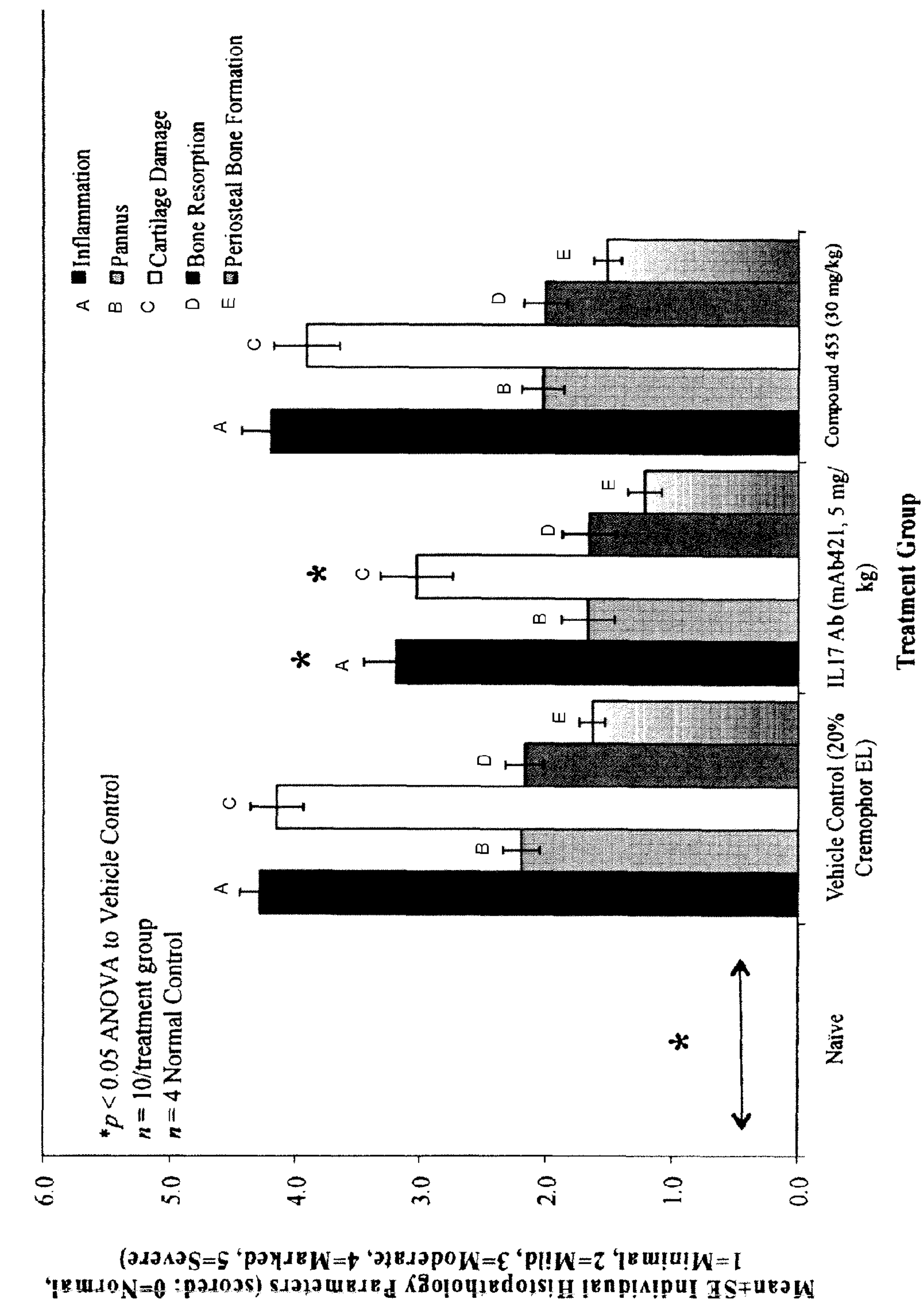

*p < 0.05 ANOVA to Vehicle Control
n = 10/treatment group
n = 4 Normal Control
MEAN ± SE CLINICAL ARTHRITIS SCORE WITH AUC CALCULATION
40
35
30
25
20
15
10
5
0
*
100%
0%
25%
11%
Naïve
Vehicle Control (20% Cremophor EL) PO, QD
IL 17 Ab (mAb421, 5 mg/kg) IP, Q2D
Compound 453 (30 mg/kg) PO, QD
TREATMENT GROUP

FIG. 7

FIG. 8


*p < 0.05 ANOVA to Vehicle Control
n = 10/treatment group
n = 4 Normal Control
A Inflammation
B Pannus
C Cartilage Damage
D Bone Resorption
E Periosteal Bone Formation
Naive
Vehicle Control (20% Cremophor EL)
IL17 Ab (mAb421, 5 mg/kg)
Compound 453 (30 mg/kg)
Treatment Group
Mean±SE Individual Histopathology Parameters (scored: 0=Normal, 1=Minimal, 2=Mild, 3=Moderate, 4=Marked, 5=Severe)
0.0
1.0
2.0
3.0
4.0
5.0
6.0

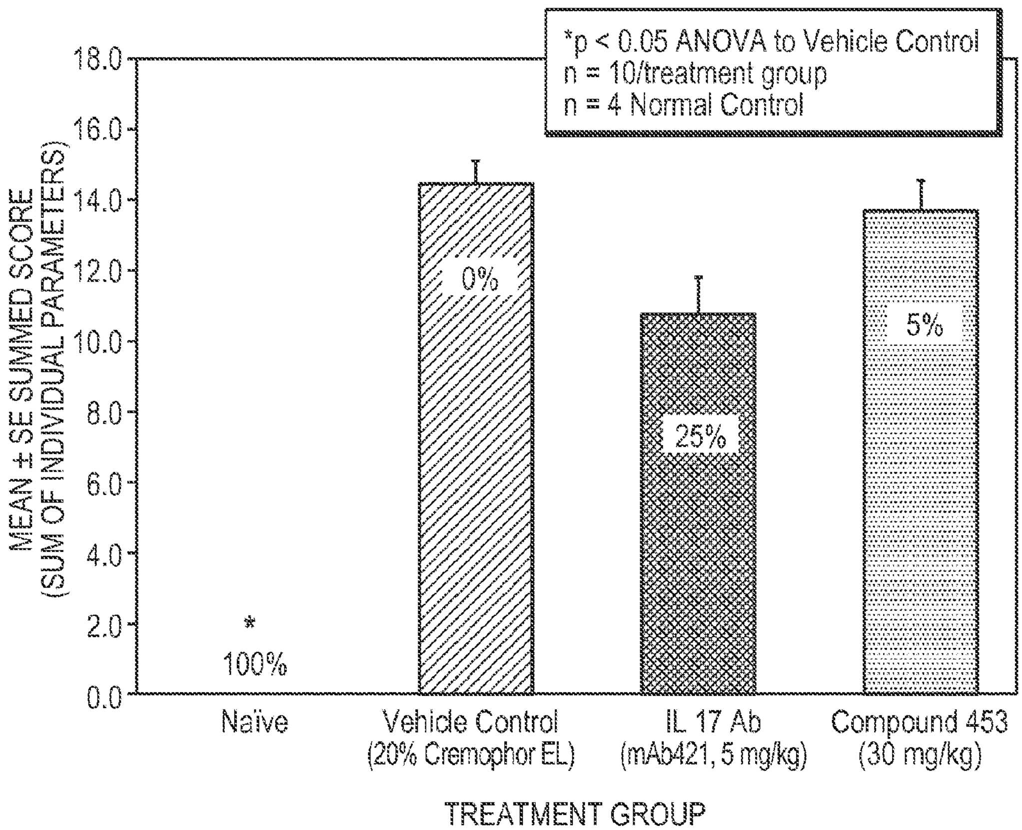
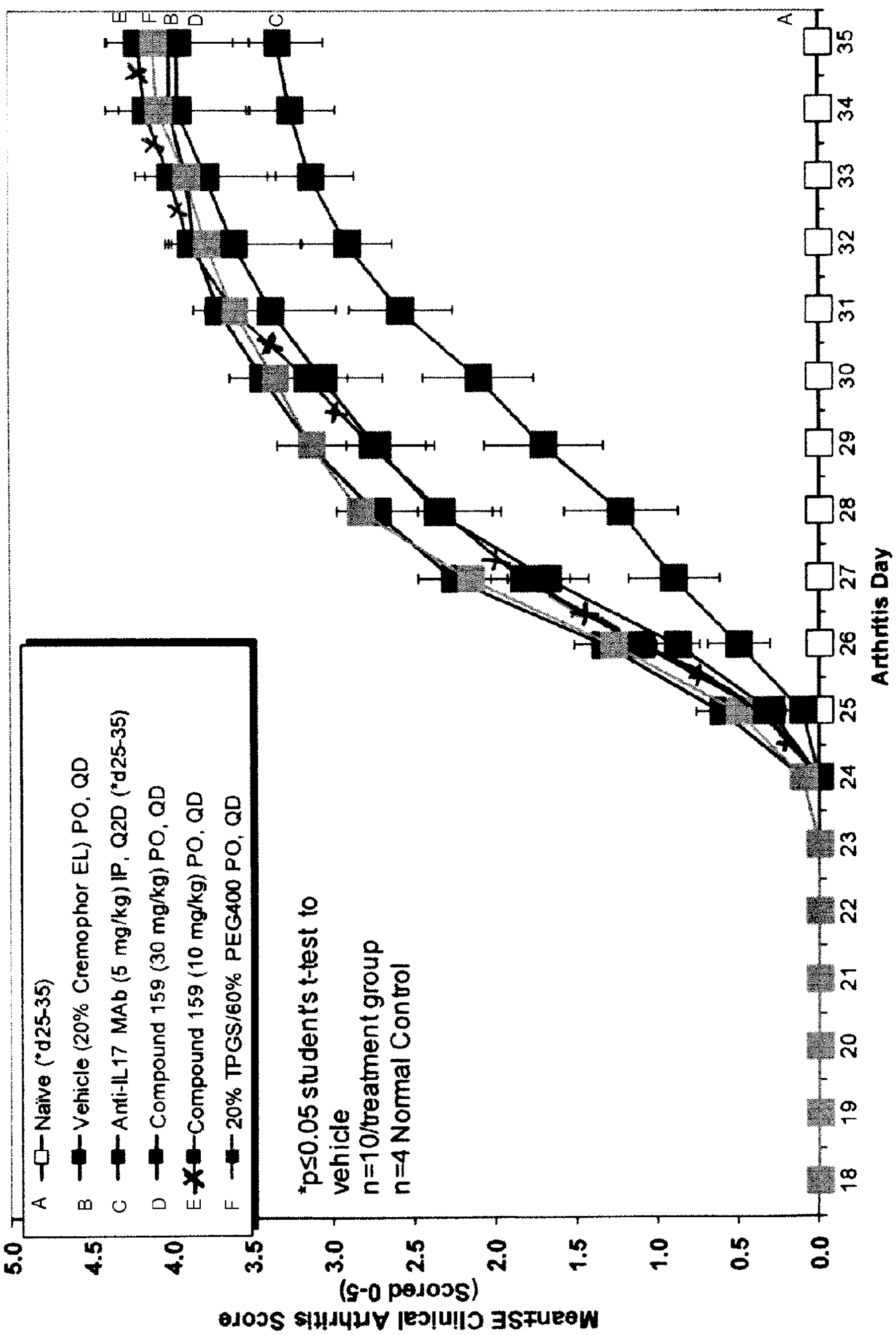

*p < 0.05 ANOVA to Vehicle Control
n = 10/treatment group
n = 4 Normal Control
MEAN ± SE SUMMED SCORE
(SUM OF INDIVIDUAL PARAMETERS)
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
*
100%
0%
25%
5%
Naïve
Vehicle Control
(20% Cremophor EL)
IL 17 Ab
(mAb421, 5 mg/kg)
Compound 453
(30 mg/kg)
TREATMENT GROUP

FIG. 9

FIG. 10


A —□— Naïve (*d25-35)
B —■— Vehicle (20% Cremophor EL) PO, QD
C —■— Anti-IL17 MAb (5 mg/kg) IP, Q2D (*d25-35)
D —■— Compound 159 (30 mg/kg) PO, QD
E —✱■— Compound 159 (10 mg/kg) PO, QD
F —■— 20% TPGS/60% PEG400 PO, QD
*p≤0.05 student's t-test to vehicle
n=10/treatment group
n=4 Normal Control
Mean±SE Clinical Arthritis Score (Scored 0-5)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
Arthritis Day
E
F
B
D
C
A

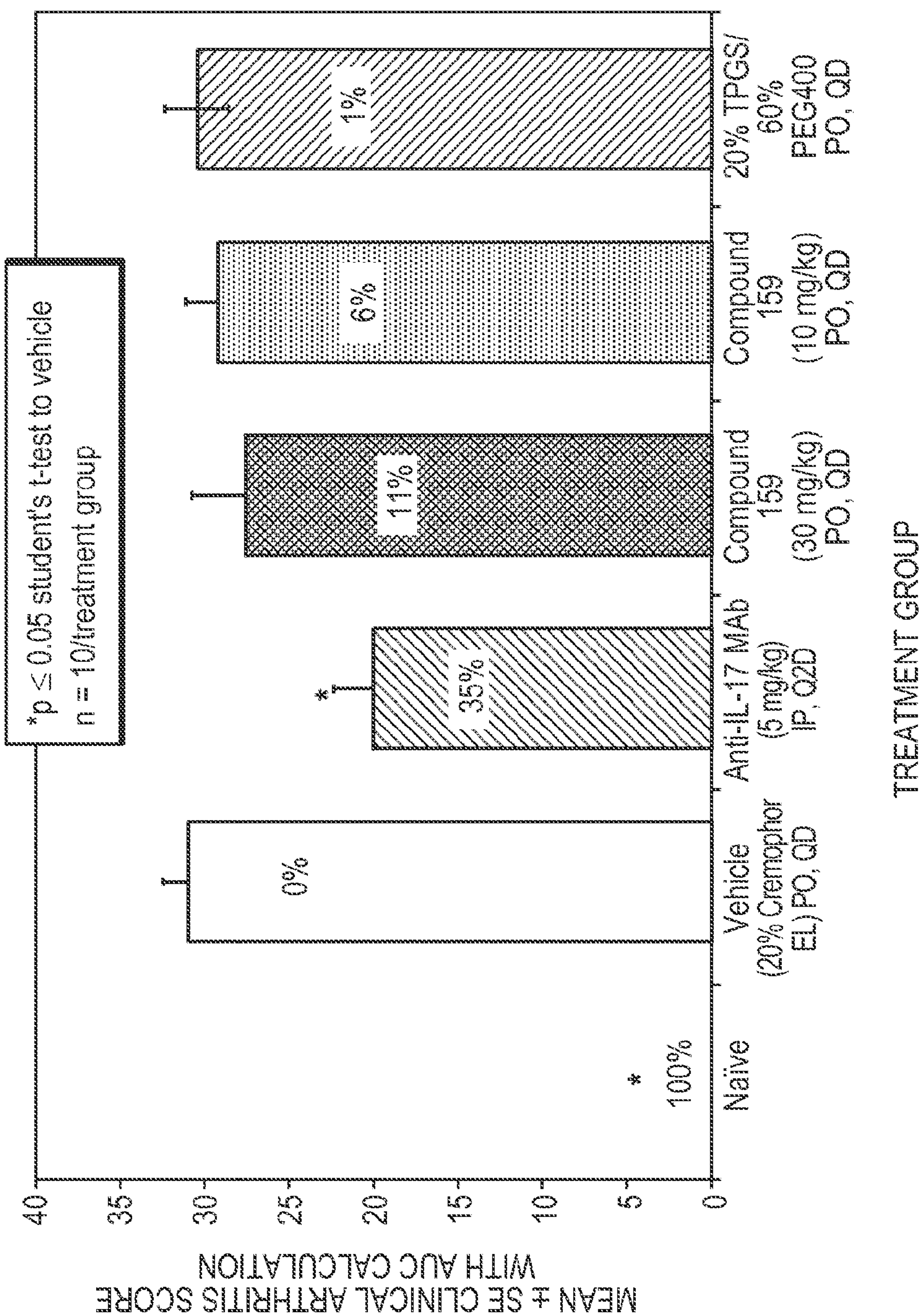

*p ≤ 0.05 student's t-test to vehicle
n = 10/treatment group
MEAN ± SE CLINICAL ARTHRITIS SCORE WITH AUC CALCULATION
0
5
10
15
20
25
30
35
40
*
100%
0%
*
35%
11%
6%
1%
Naïve
Vehicle (20% Cremophor EL) PO, QD
Anti-IL-17 MAb (5 mg/kg) IP, Q2D
Compound 159 (30 mg/kg) PO, QD
Compound 159 (10 mg/kg) PO, QD
20% TPGS/ 60% PEG400 PO, QD
TREATMENT GROUP

FIG. 11

Figure 12

Table 1. Exemplary Compounds of the Invention

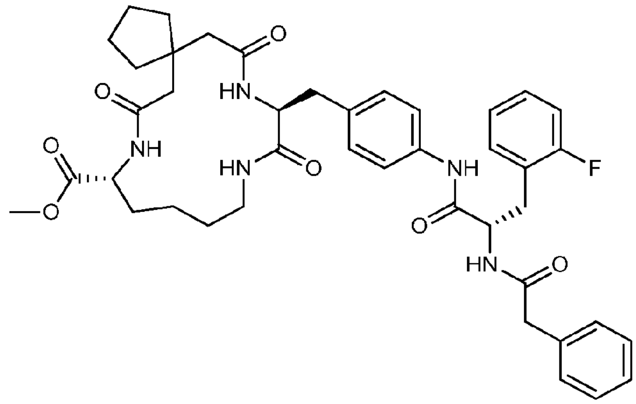
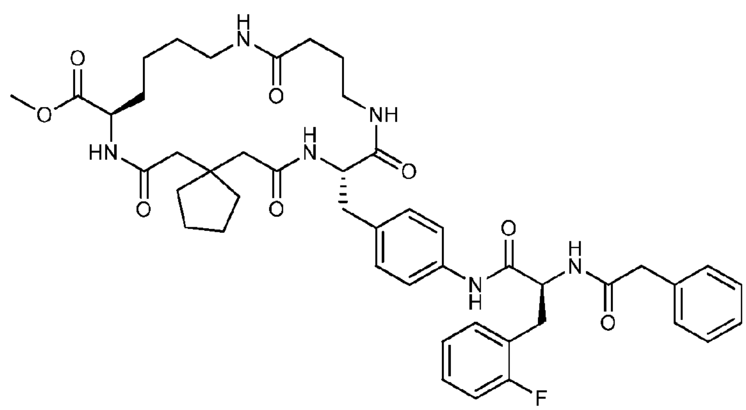
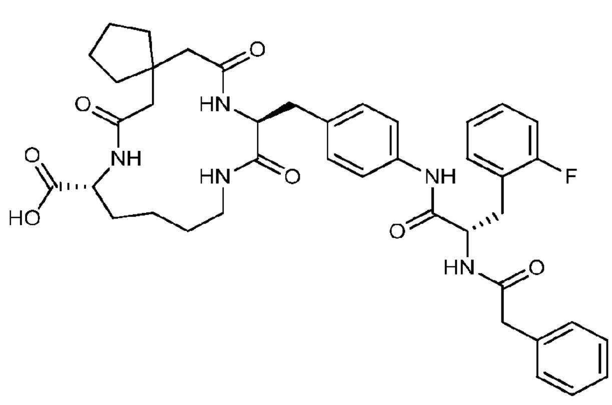
Compound No.	Structure
100	
101	
102	

FIG. 12-1

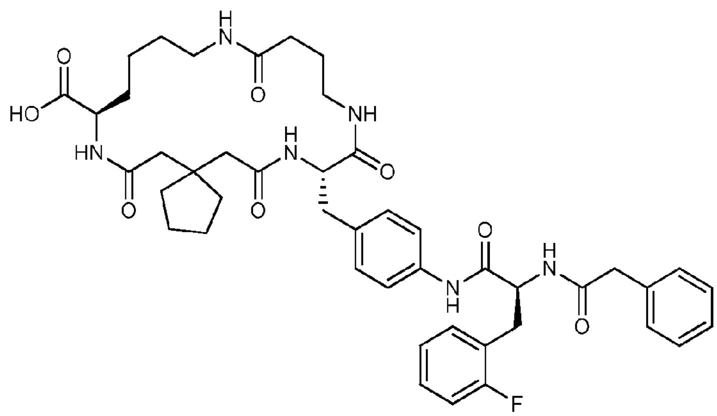
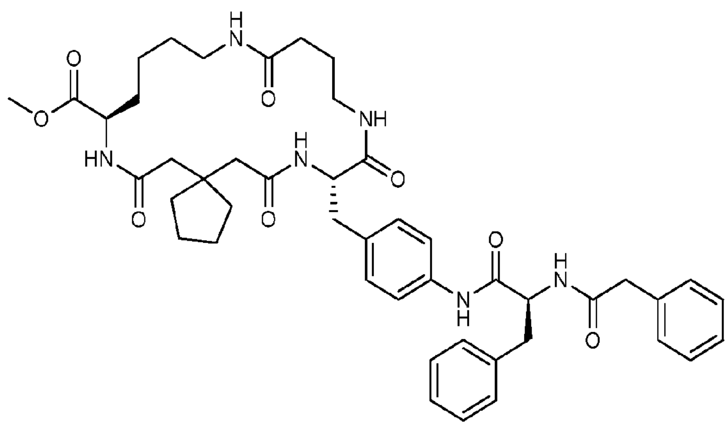
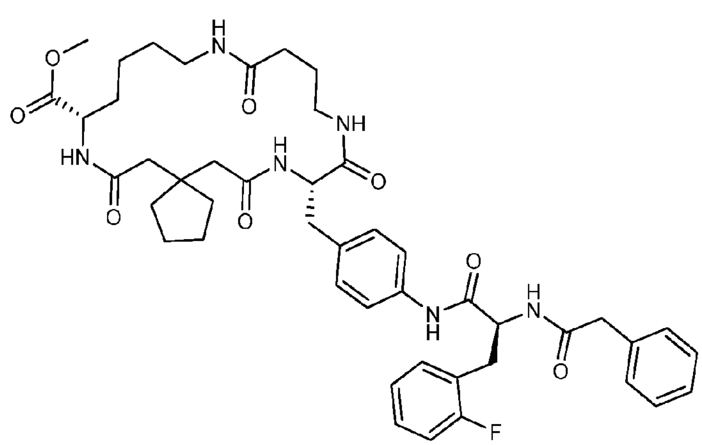
Compound No.	Structure
103	
104	
105	

FIG. 12-2

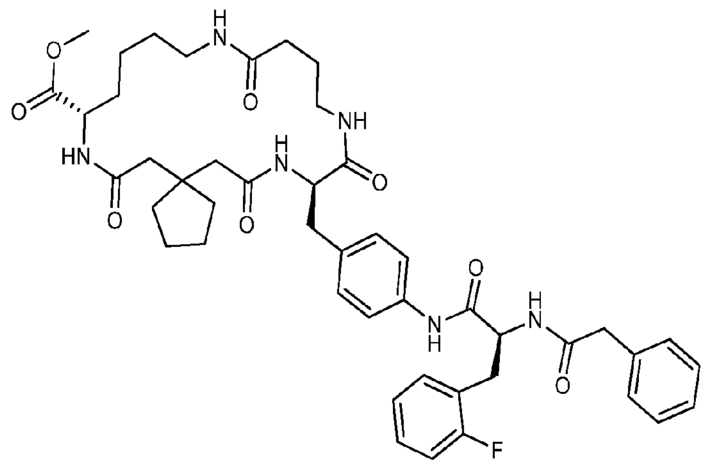
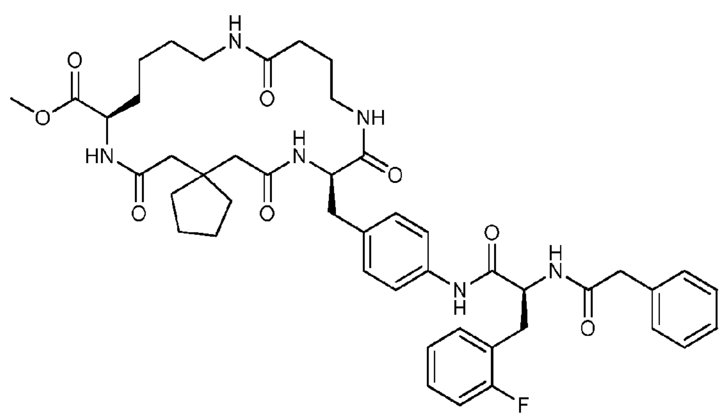
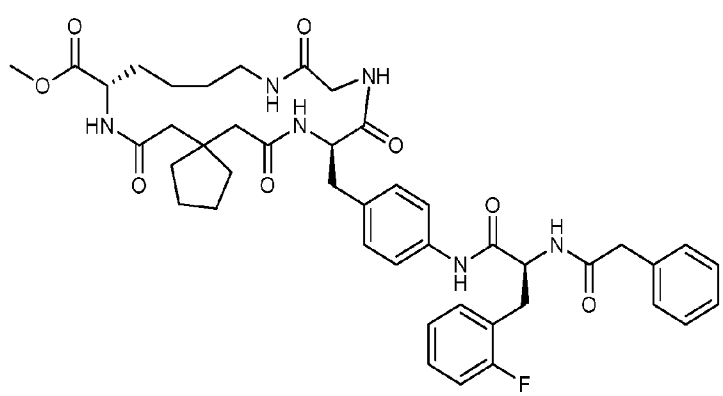
Compound No.	Structure
106	
107	
108	

FIG. 12-3

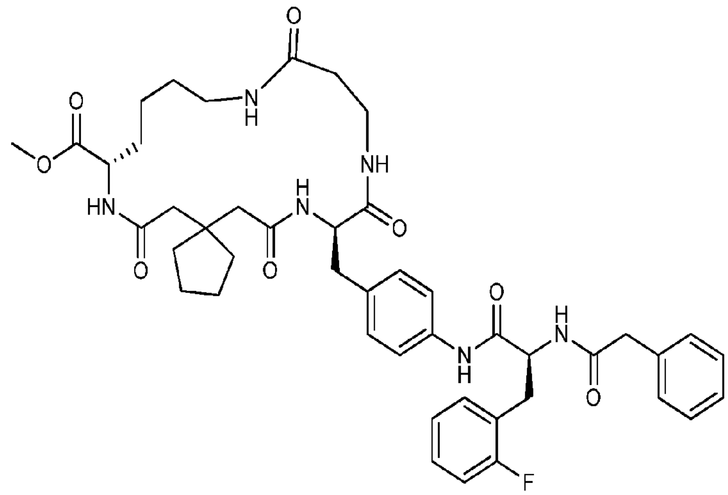
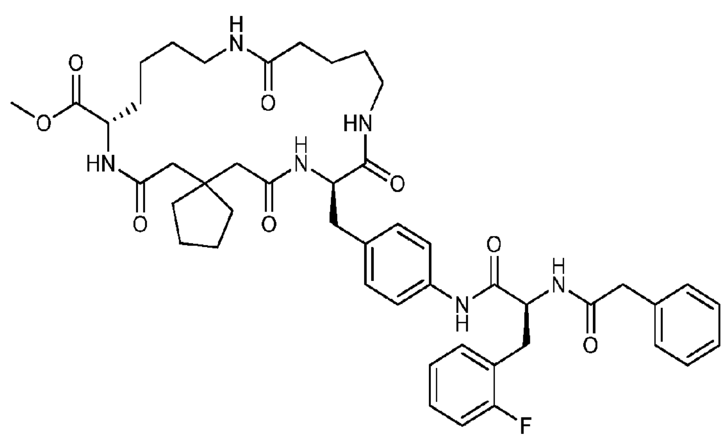
Compound No.	Structure
109	
110	

FIG. 12-4

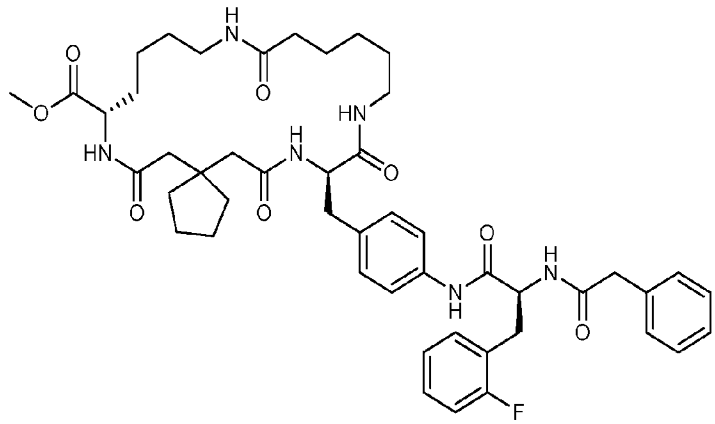
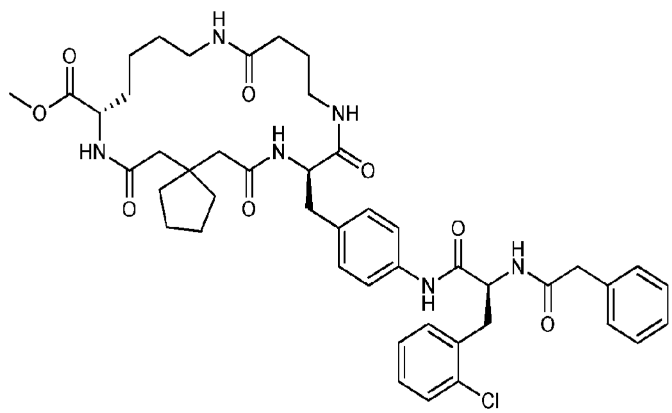
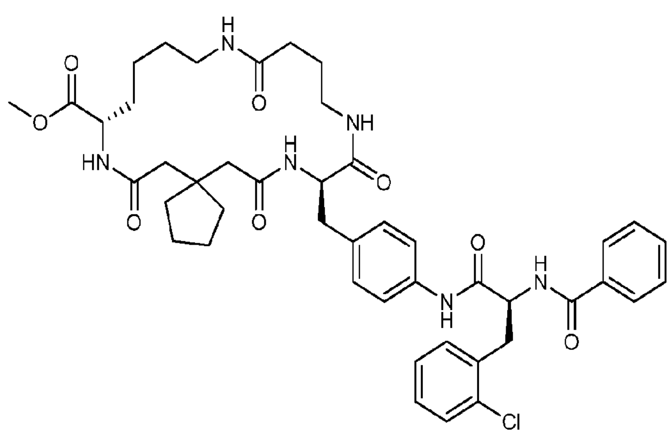
Compound No.	Structure
111	
112	
113	

FIG. 12-5

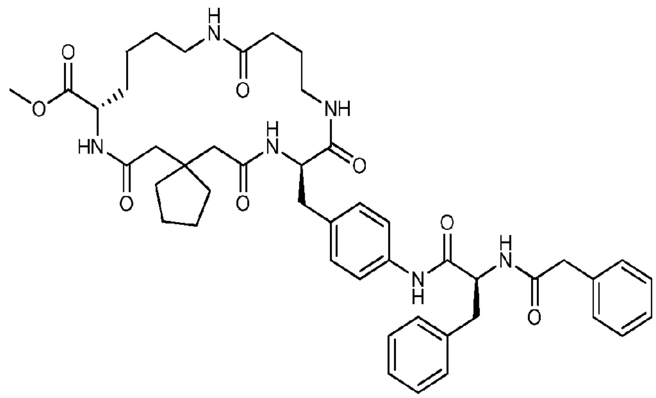
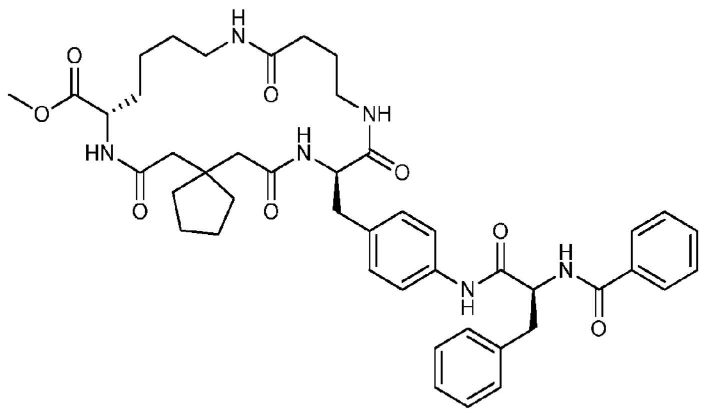
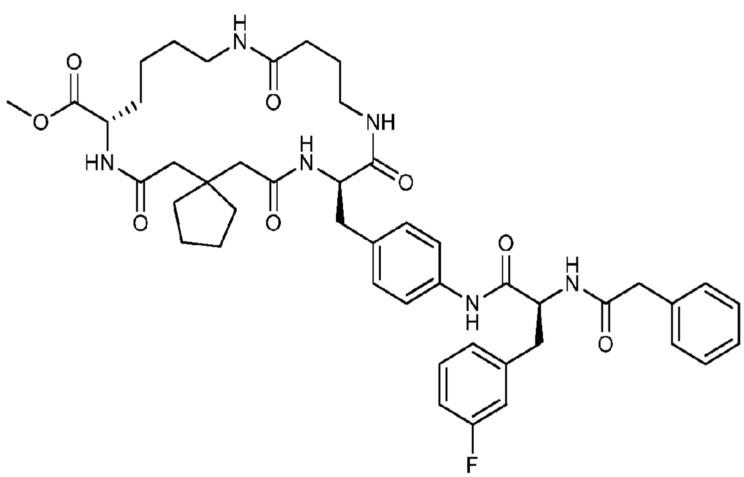
Compound No.	Structure
114	
115	
116	

FIG. 12-6

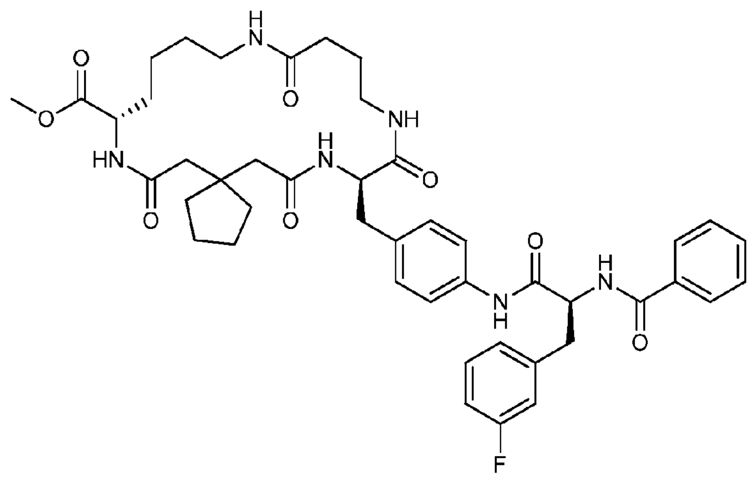
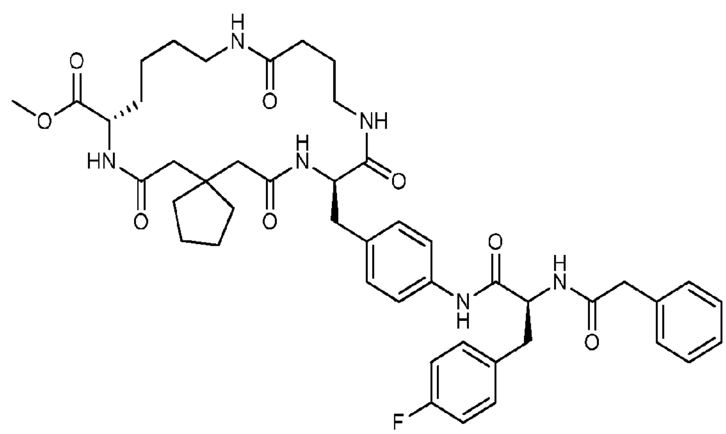
Compound No.	Structure
117	
118	

FIG. 12-7

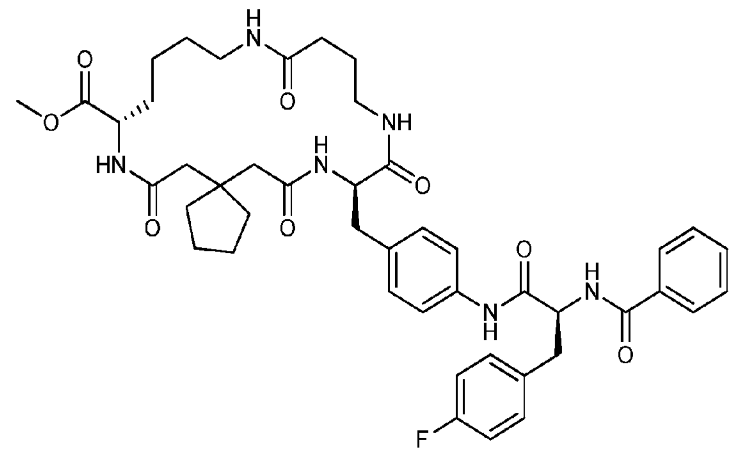
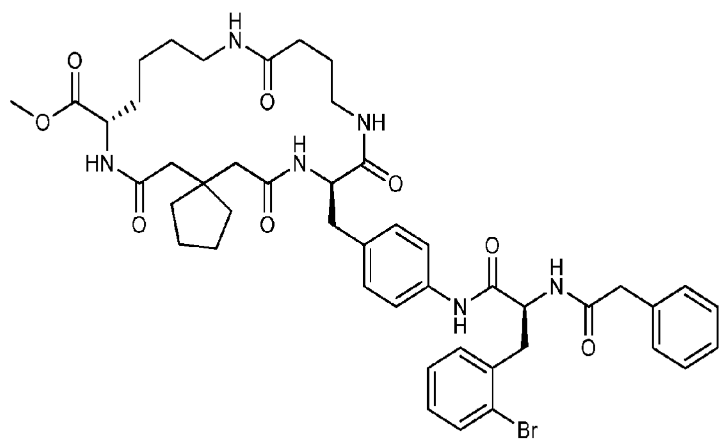
Compound No.	Structure
119	
120	

FIG. 12-8

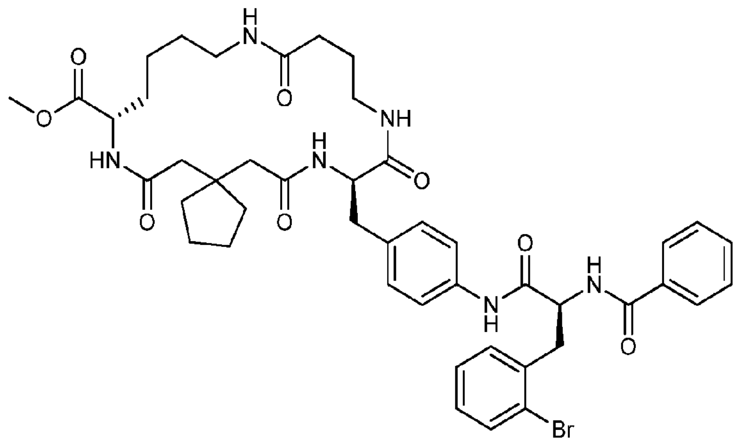
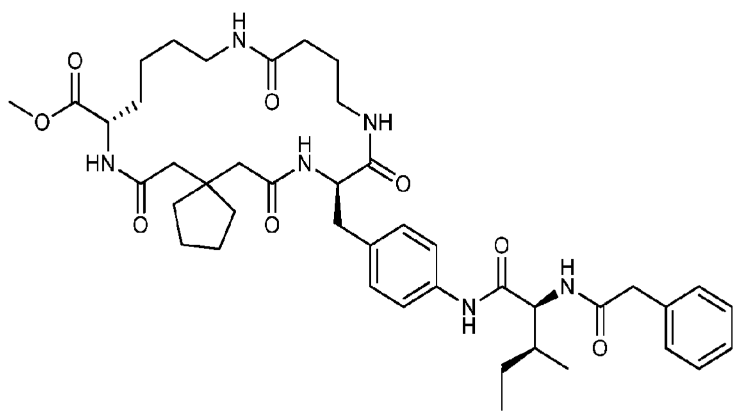
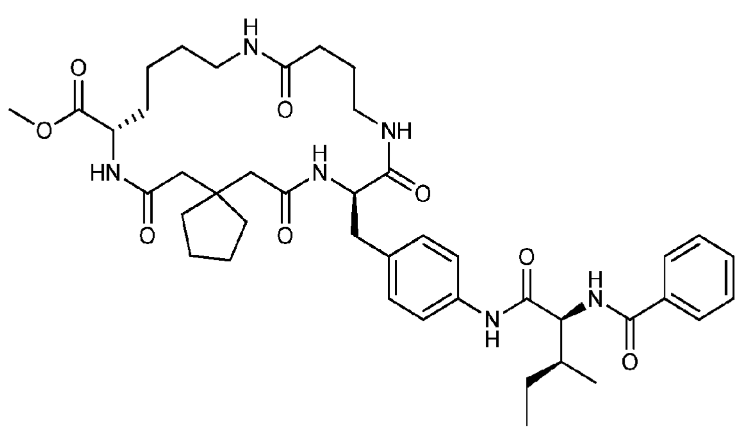
Compound No.	Structure
121	
122	
123	

FIG. 12-9

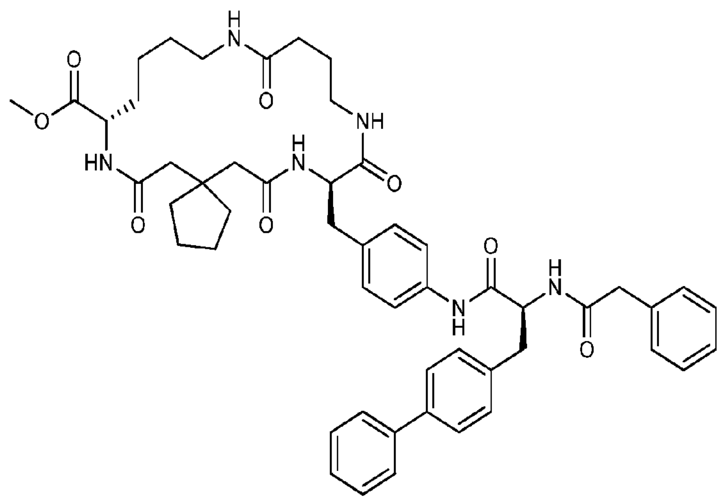
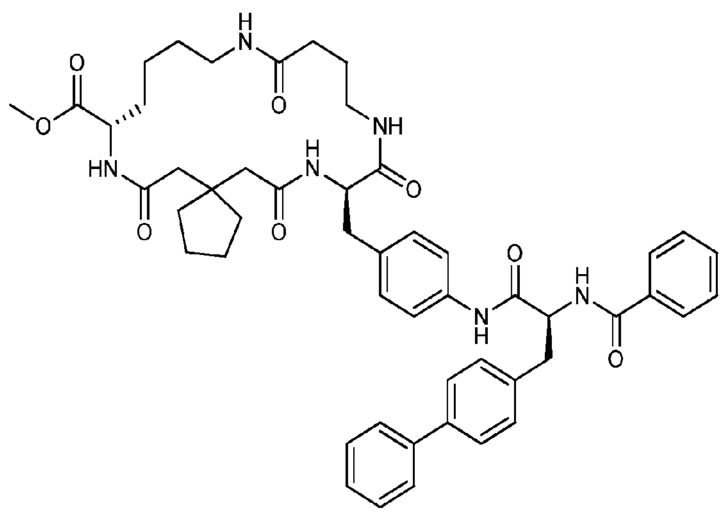
Compound No.	Structure
124	
125	

FIG. 12-10

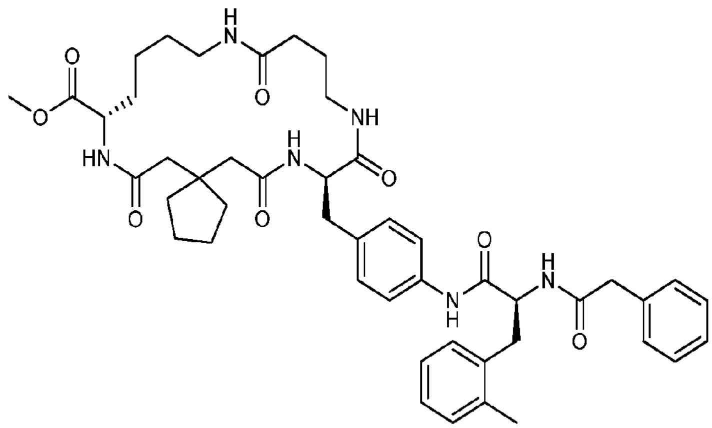
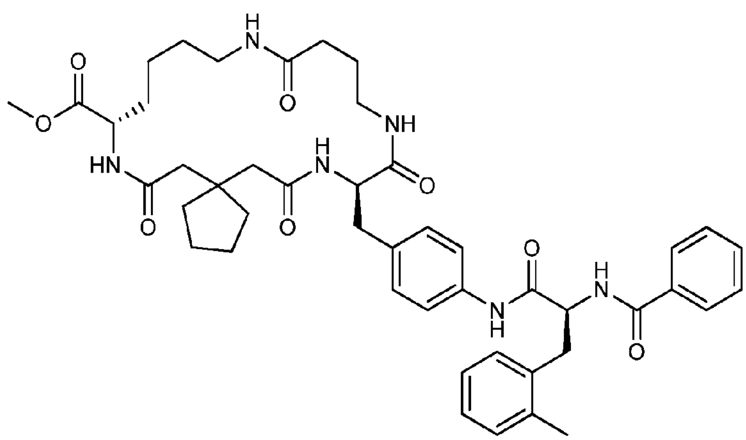
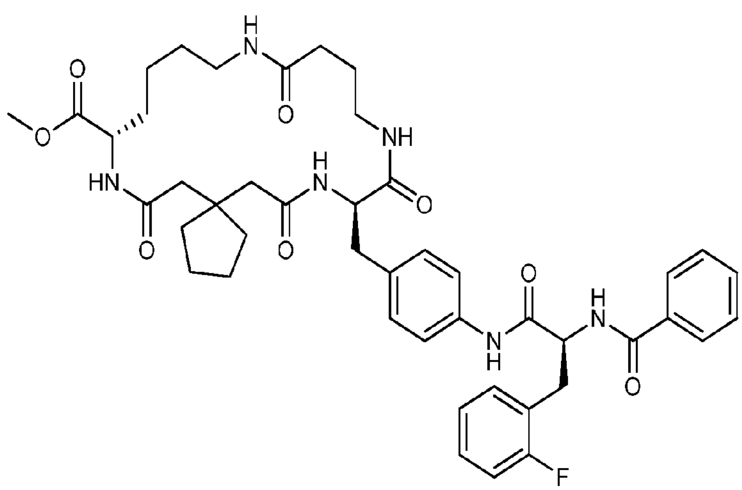
Compound No.	Structure
126	
127	
128	

FIG. 12-11

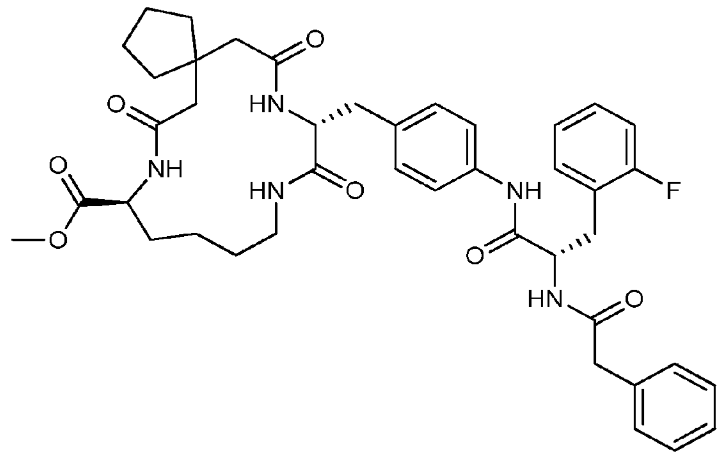
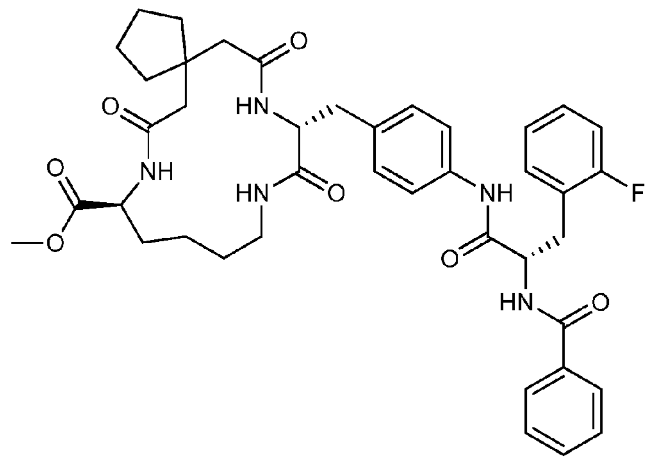
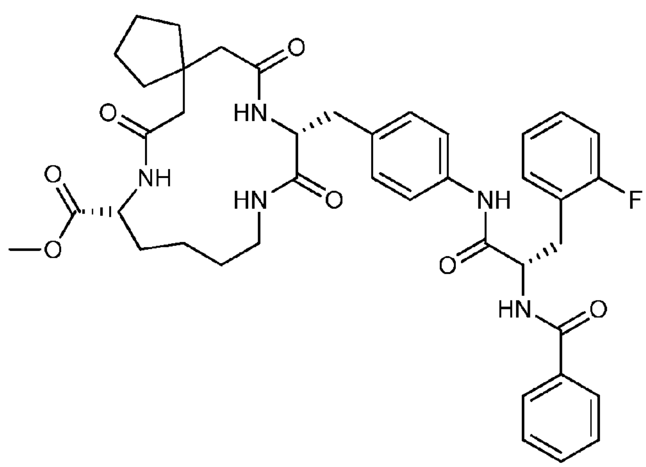
Compound No.	Structure
129	
130	
131	

FIG. 12-12

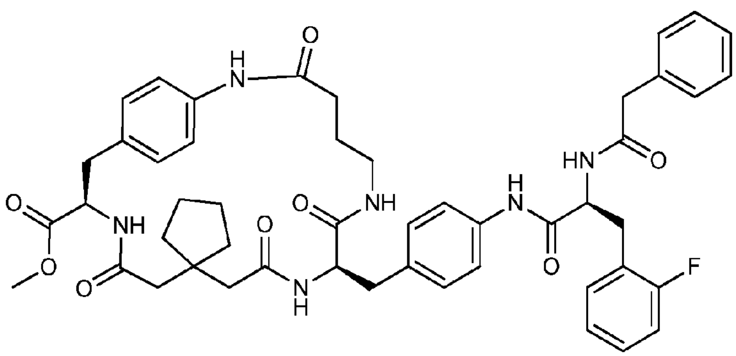
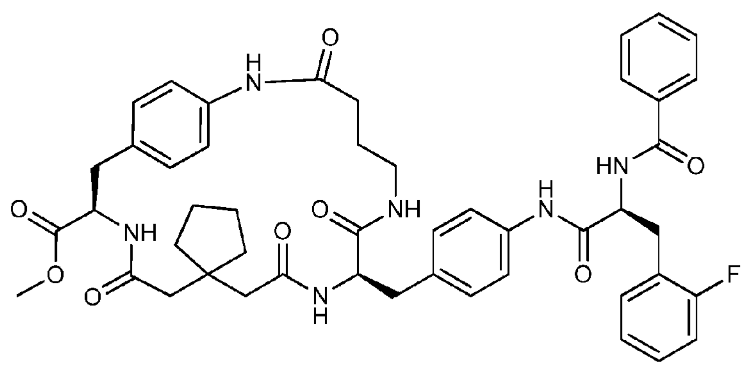
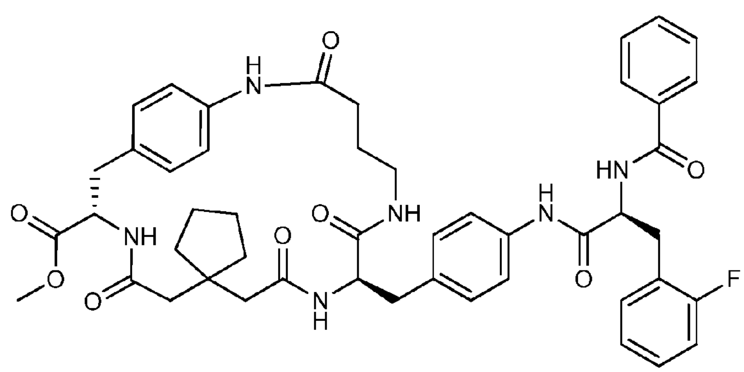
Compound No.	Structure
132	
133	
134	

FIG. 12-13

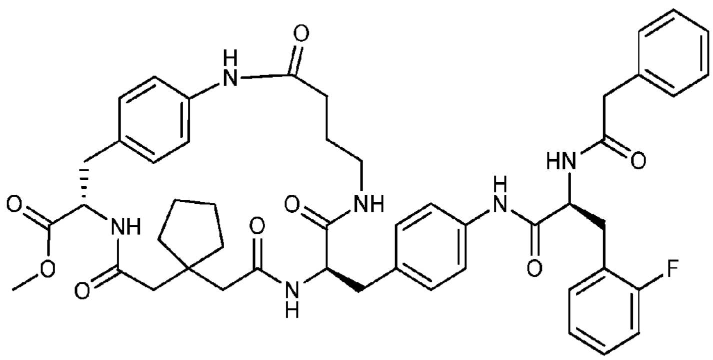
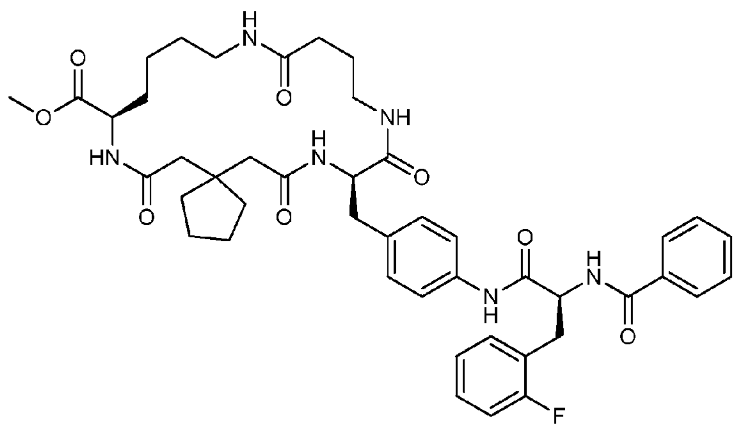
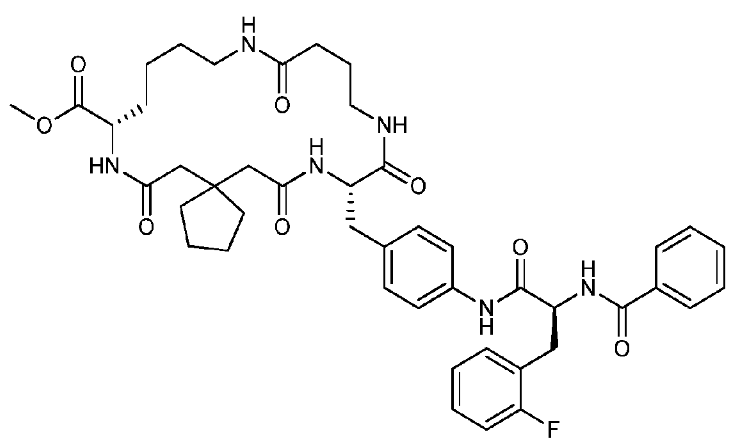
Compound No.	Structure
135	
136	
137	

FIG. 12-14

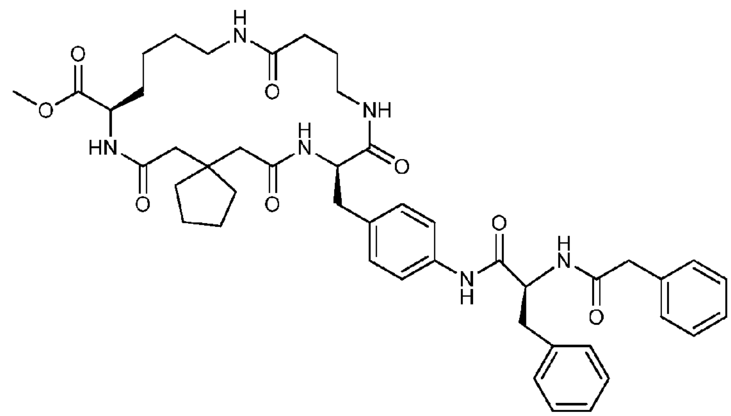
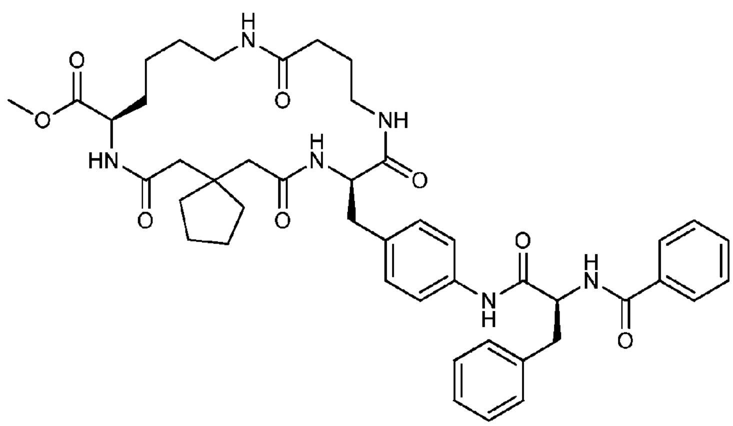
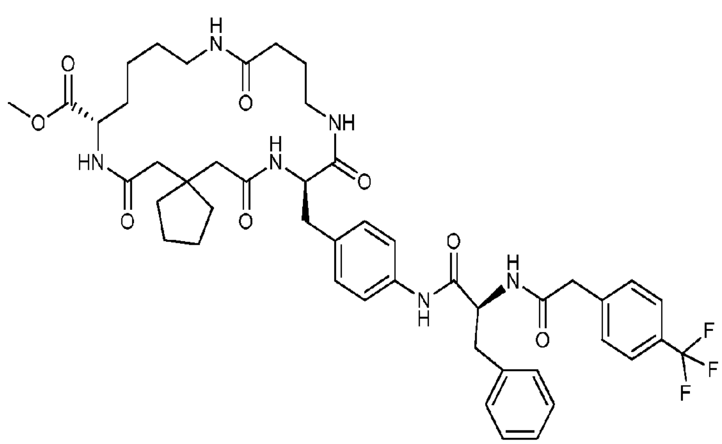
Compound No.	Structure
138	
139	
140	

FIG. 12-15

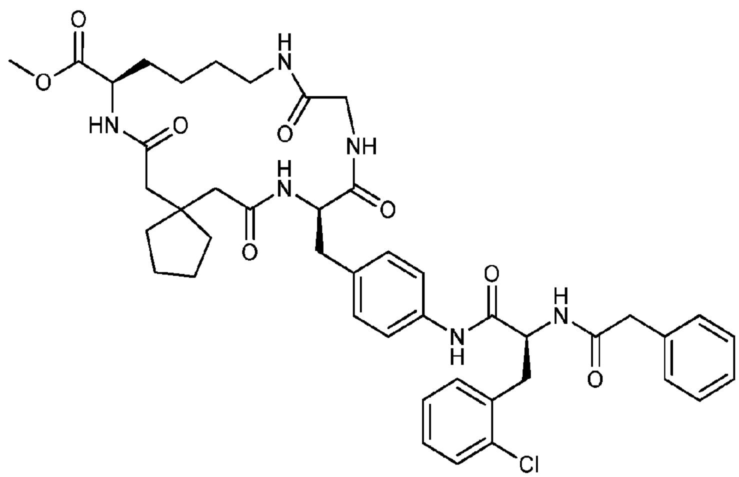
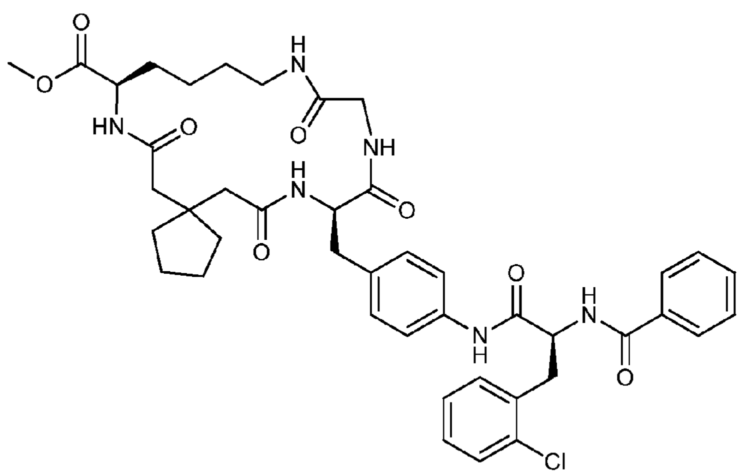
Compound No.	Structure
141	
142	

FIG. 12-16

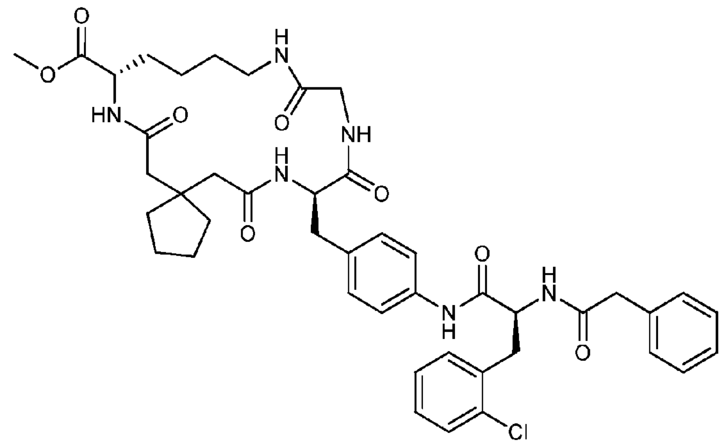
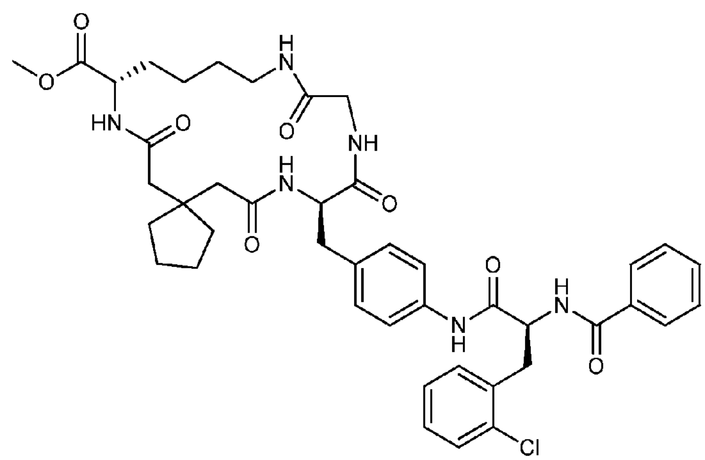
Compound No.	Structure
143	
144	

FIG. 12-17

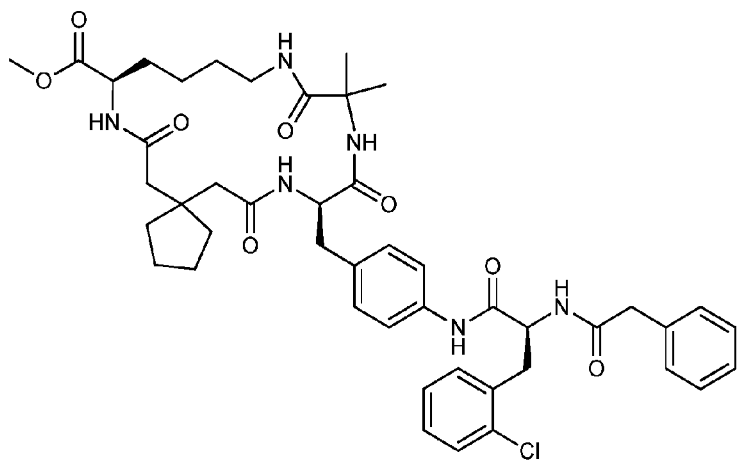
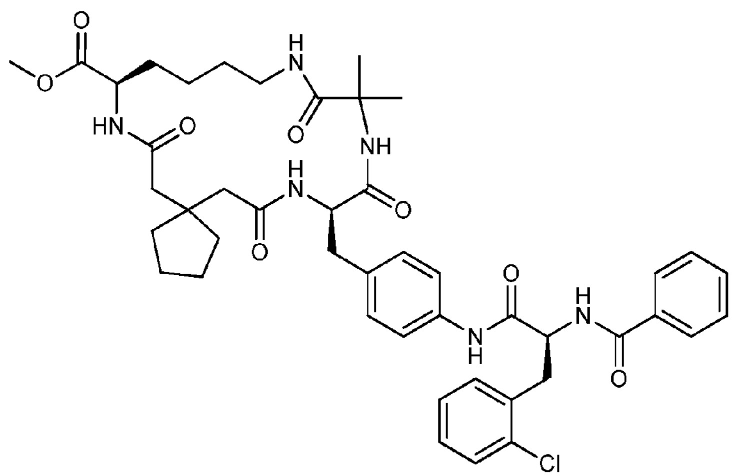
Compound No.	Structure
145	
146	

FIG. 12-18

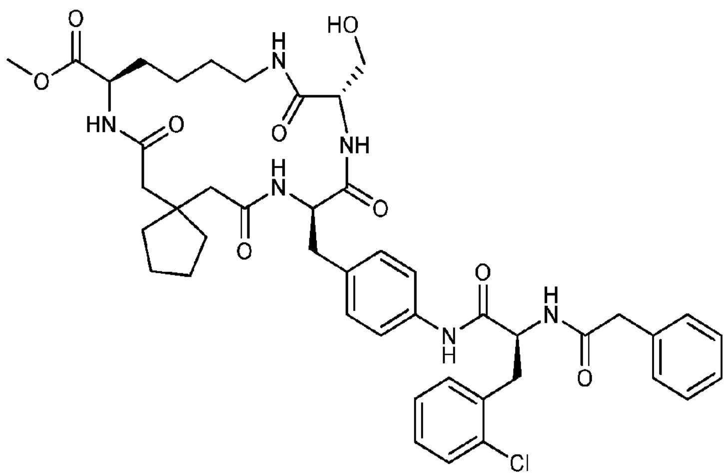
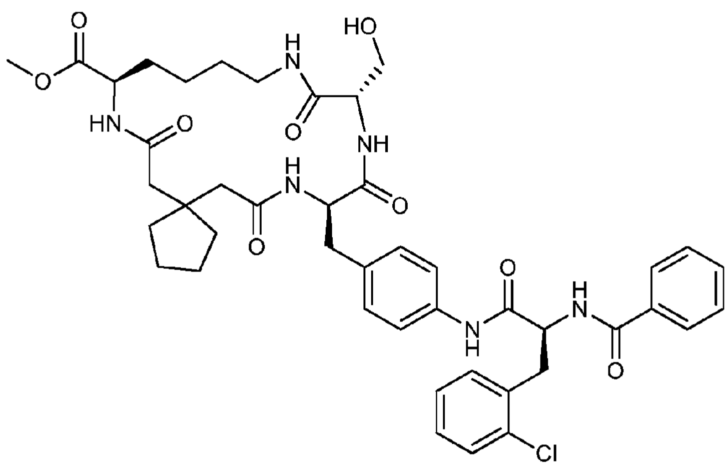
Compound No.	Structure
147	
148	

FIG. 12-19

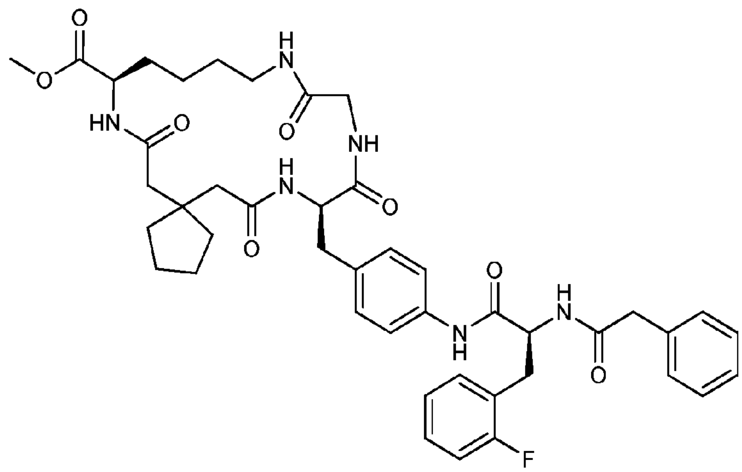
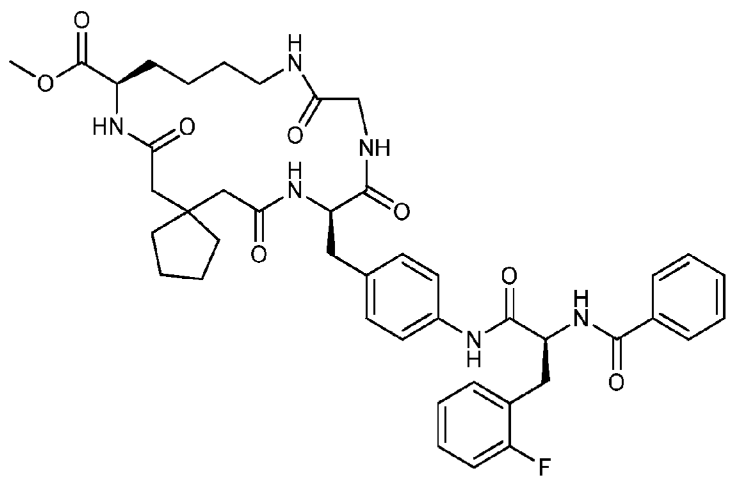
Compound No.	Structure
149	
150	

FIG. 12-20

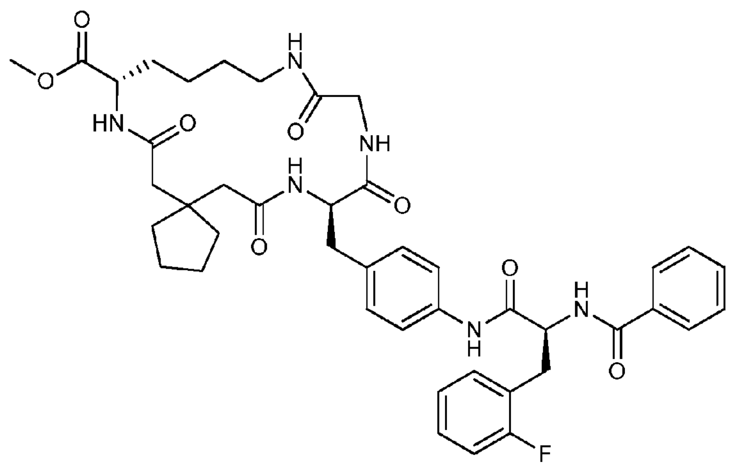
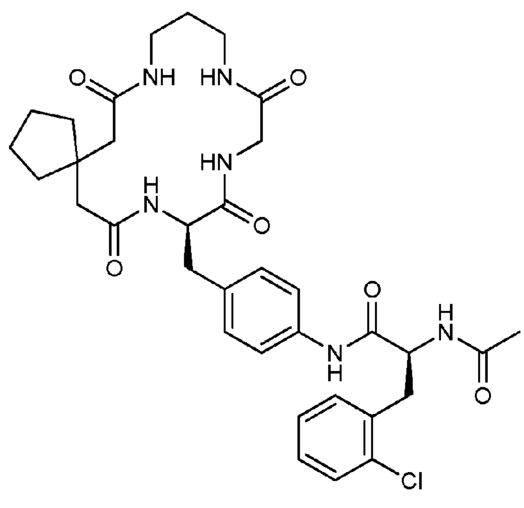
Compound No.	Structure
151	
152	

FIG. 12-21

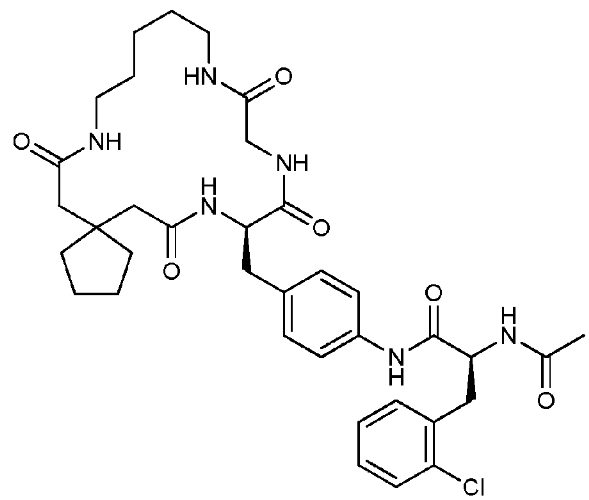
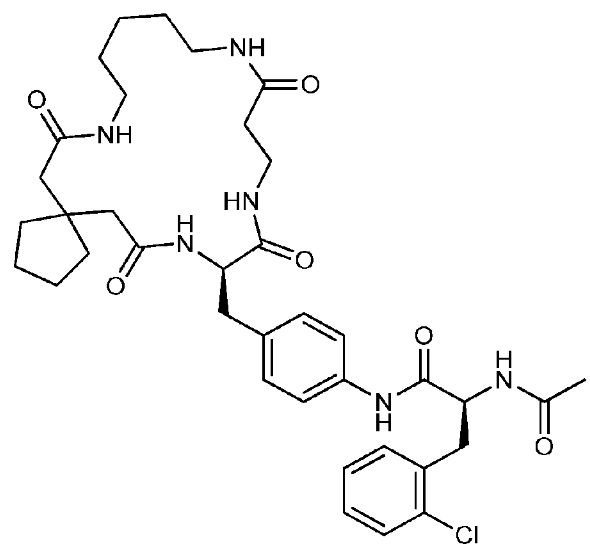
Compound No.	Structure
153	
154	

FIG. 12-22

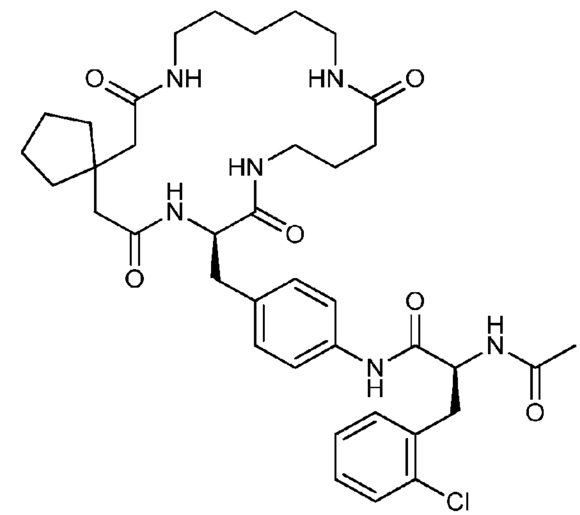
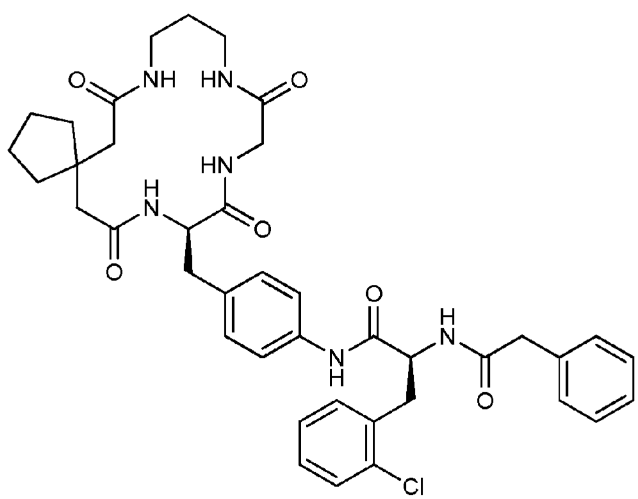
Compound No.	Structure
155	
156	

FIG. 12-23

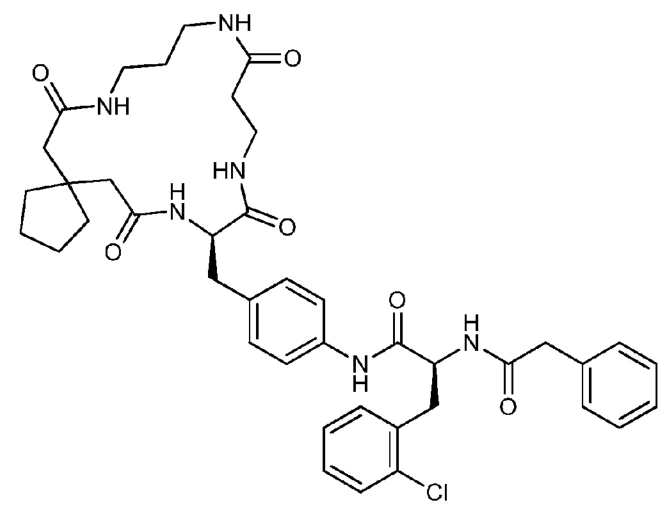
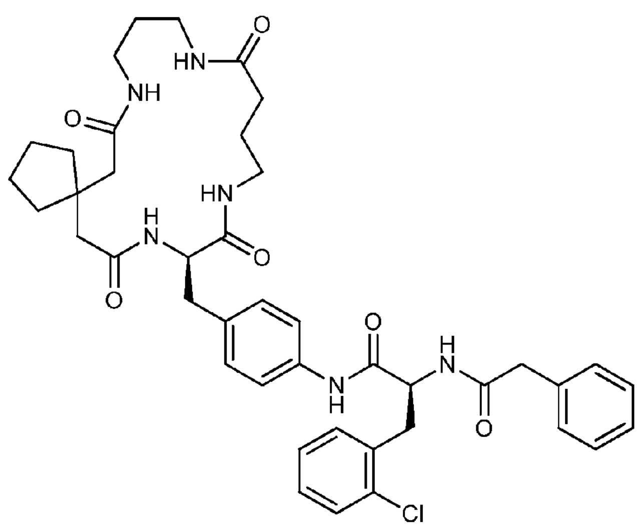
Compound No.	Structure
157	
158	

FIG. 12-24

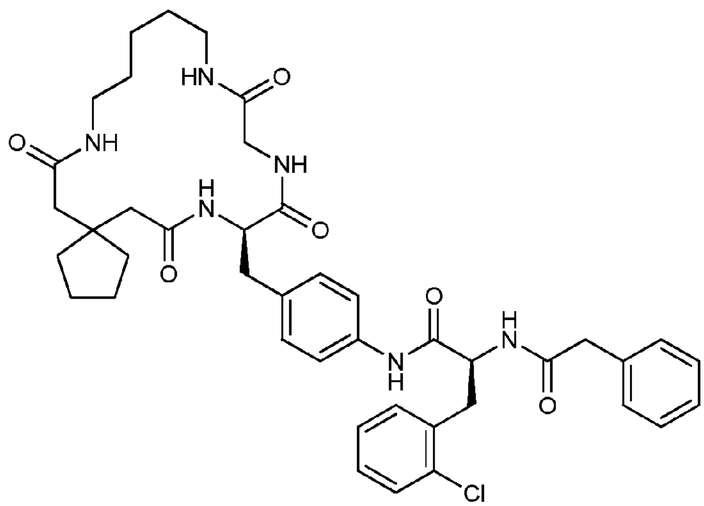
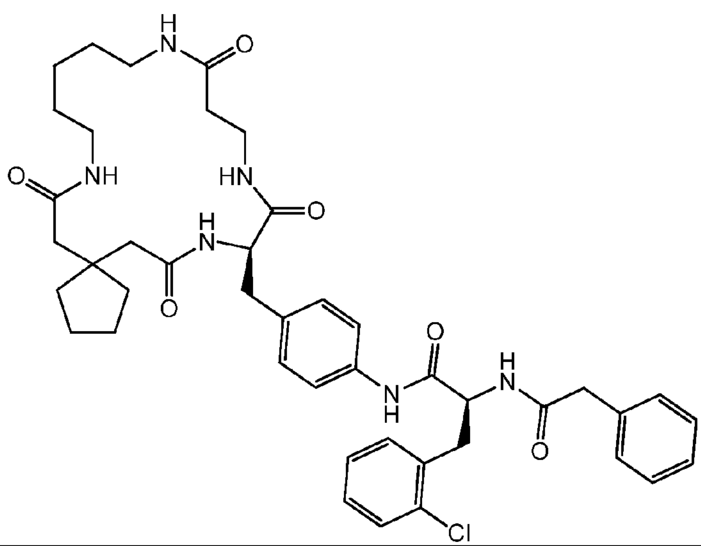
Compound No.	Structure
159	
160	

FIG. 12-25

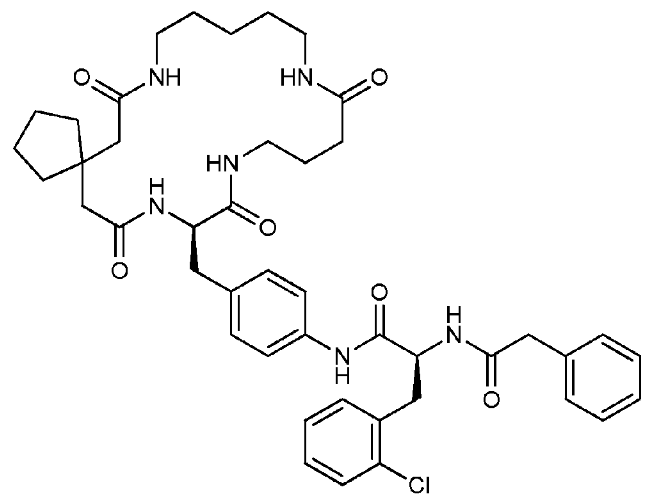
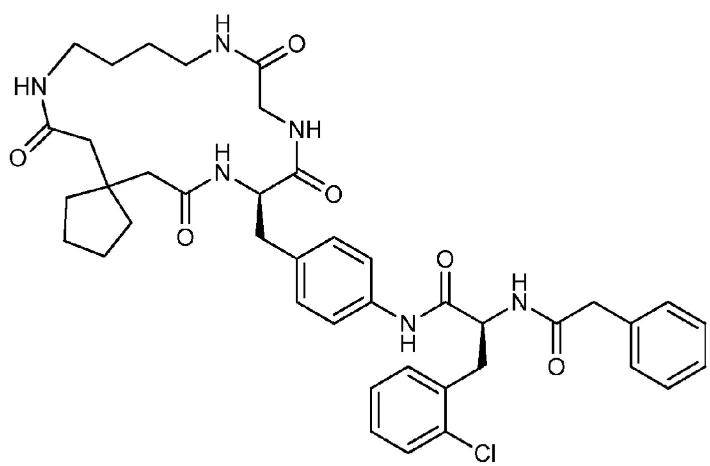
Compound No.	Structure
161	
162	

FIG. 12-26

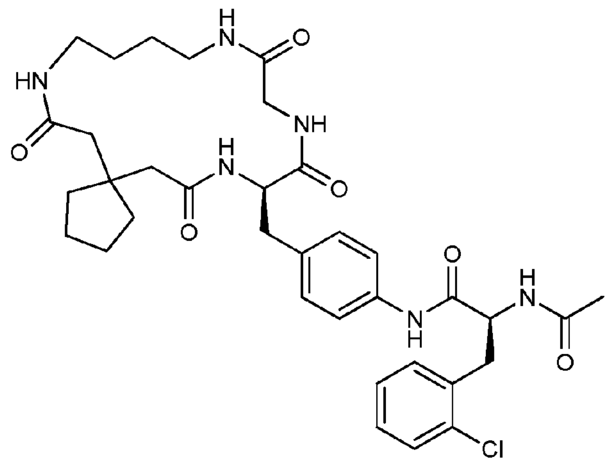
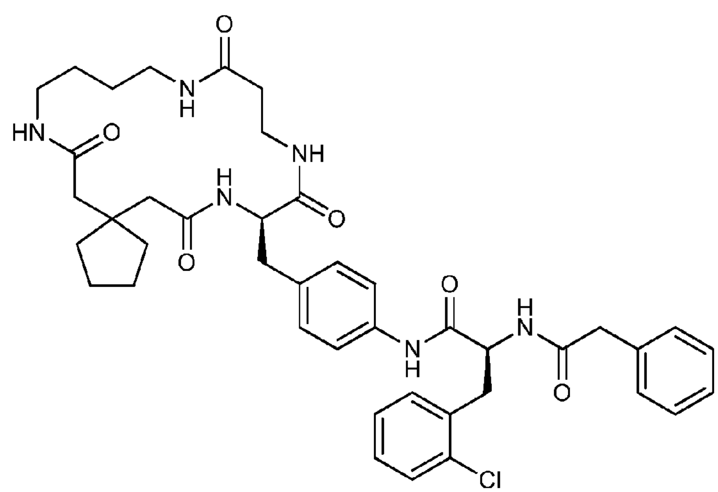
Compound No.	Structure
163	
164	

FIG. 12-27

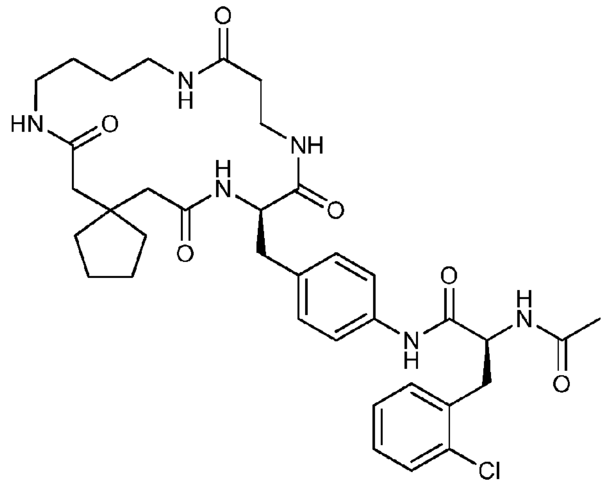
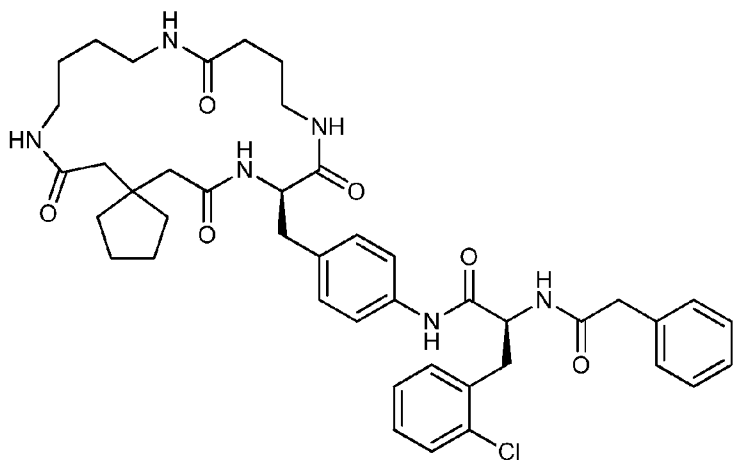
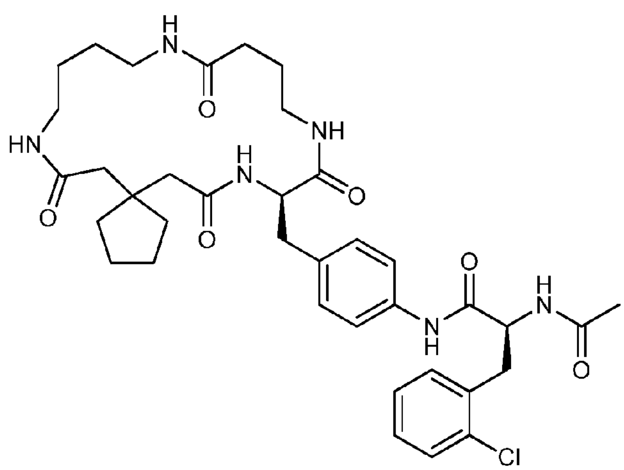
Compound No.	Structure
165	
166	
167	

FIG. 12-28

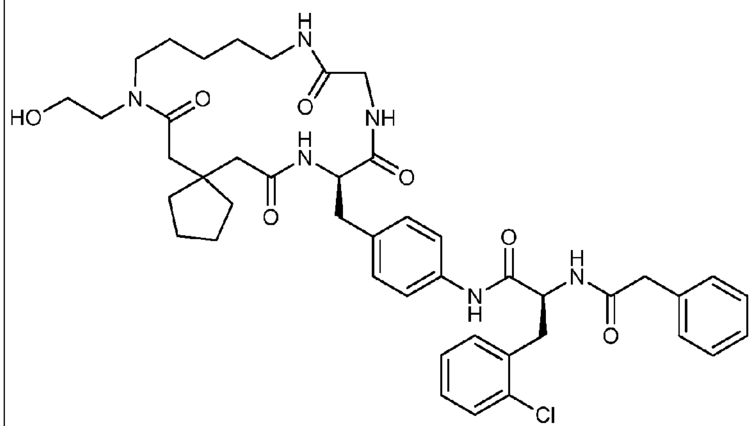
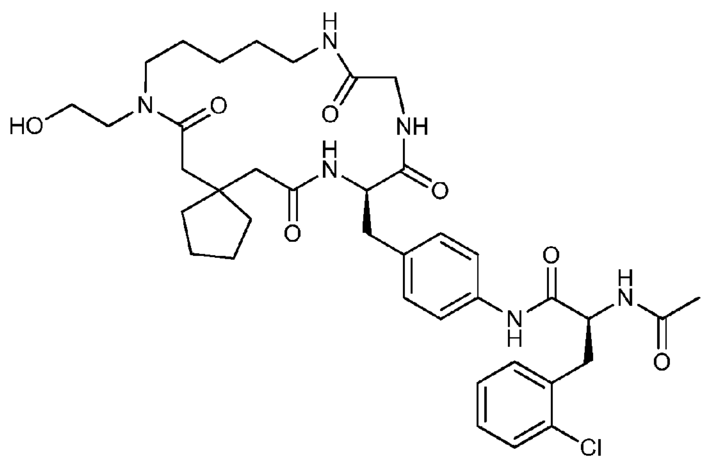
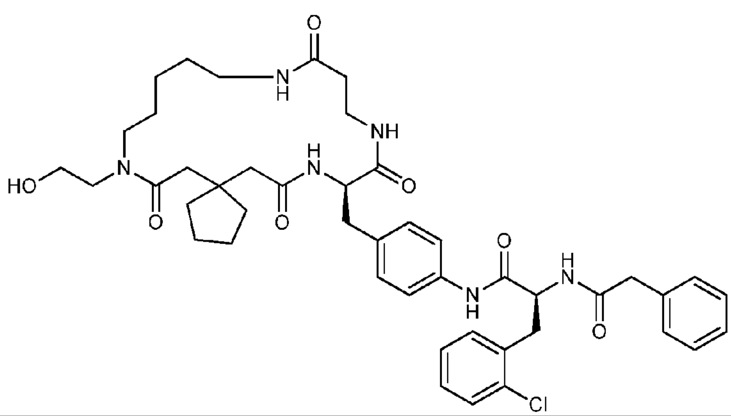
Compound No.	Structure
168	
169	
170	

FIG. 12-29

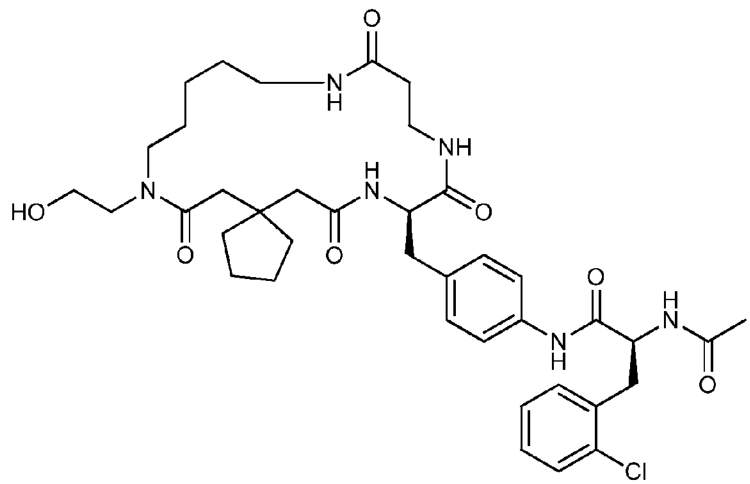
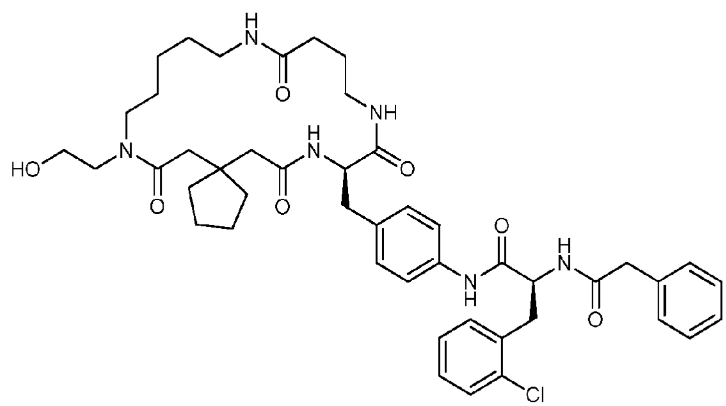
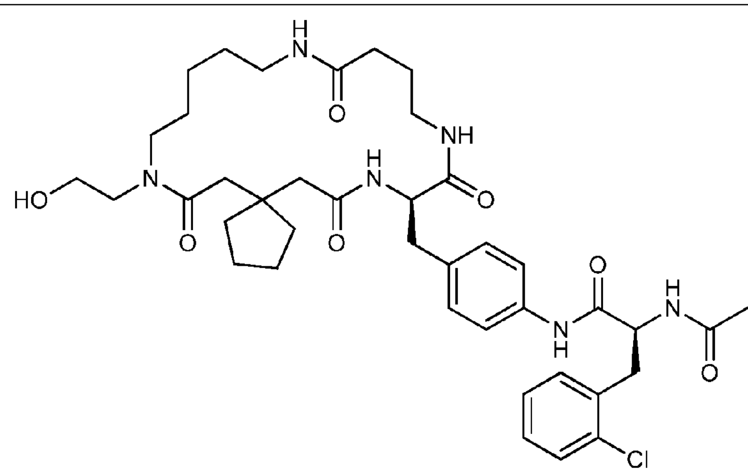
Compound No.	Structure
171	
172	
173	

FIG. 12-30

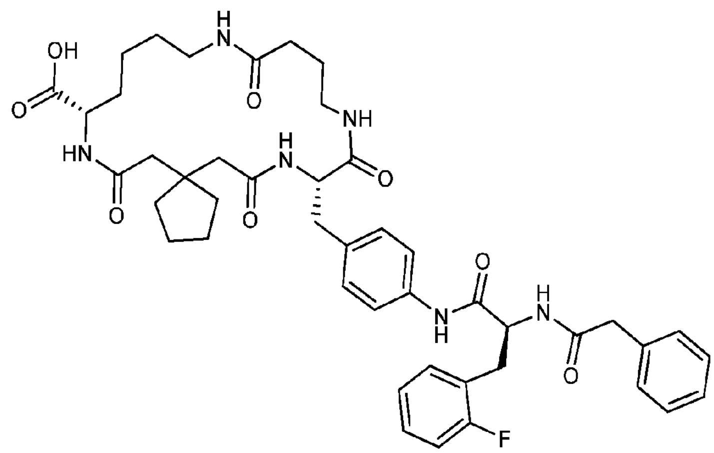
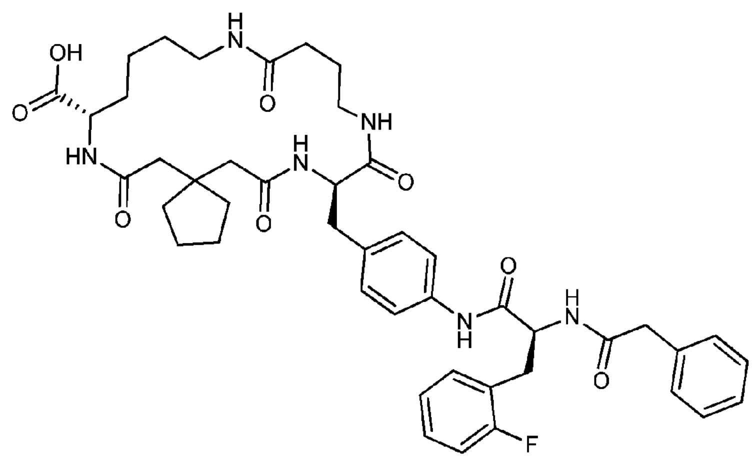
Compound No.	Structure
174	
175	

FIG. 12-31

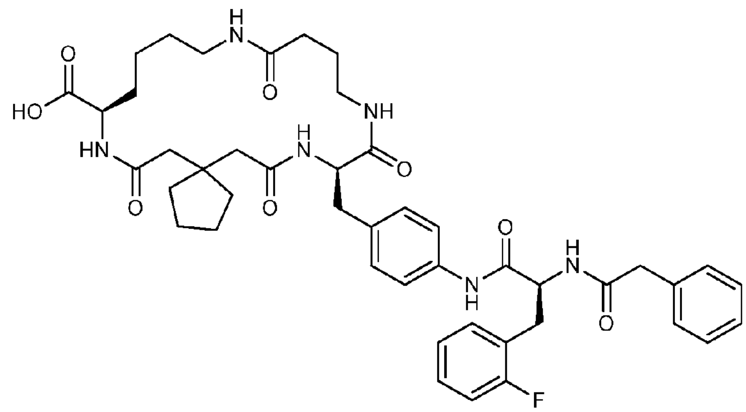
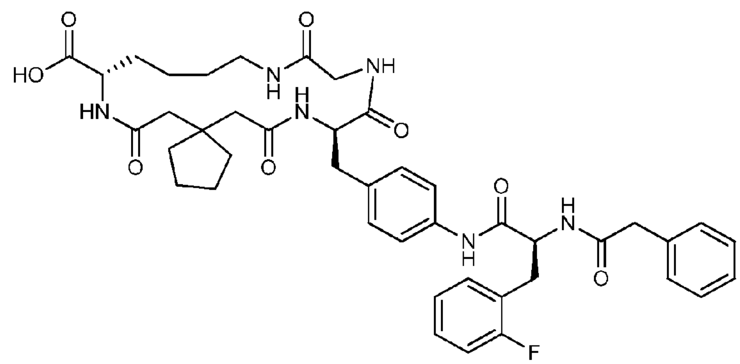
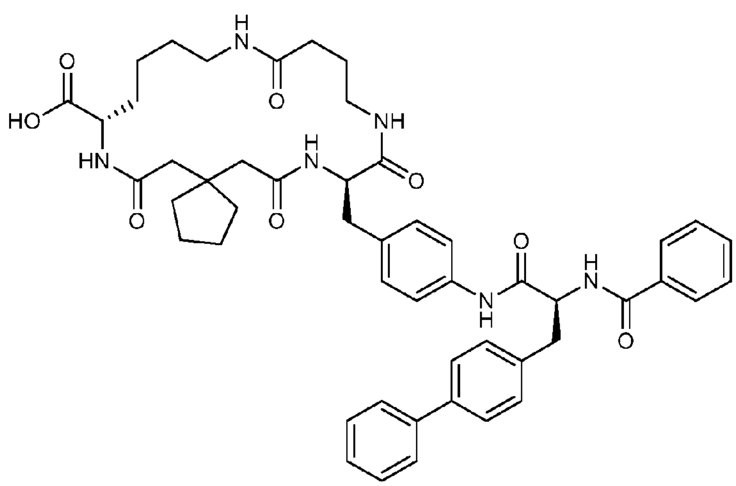
Compound No.	Structure
176	
177	
178	

FIG. 12-32

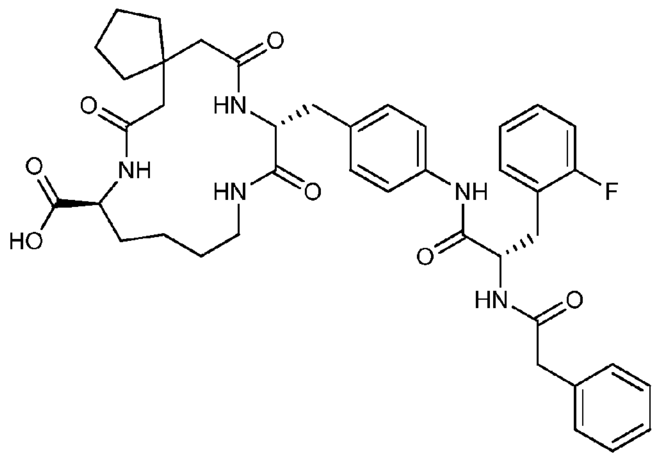
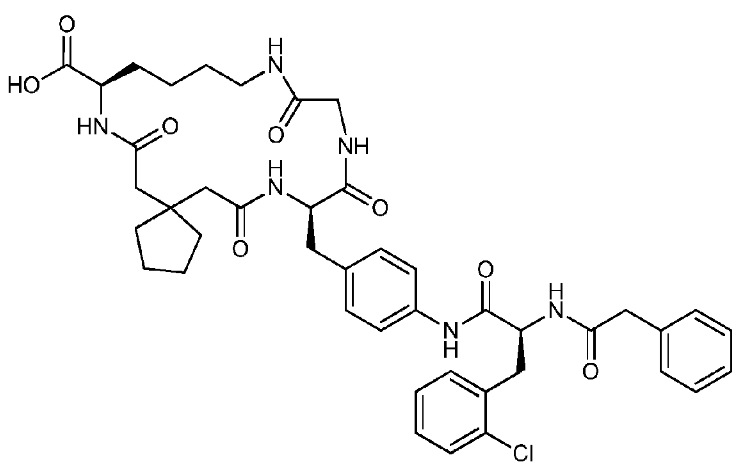
Compound No.	Structure
179	
180	

FIG. 12-33

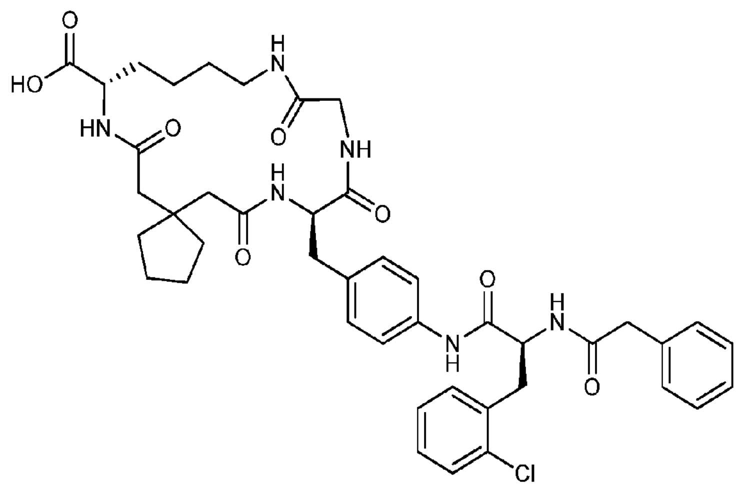
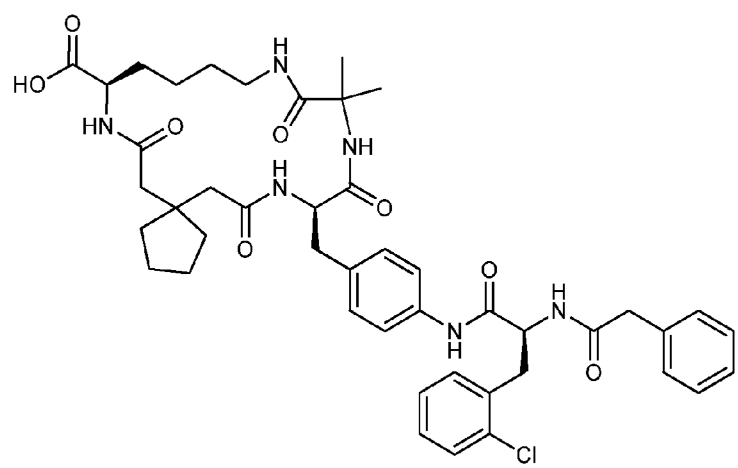
Compound No.	Structure
181	
182	

FIG. 12-34

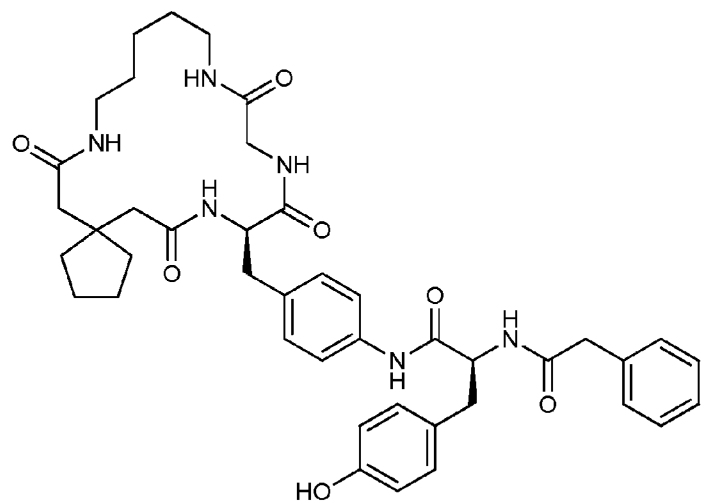
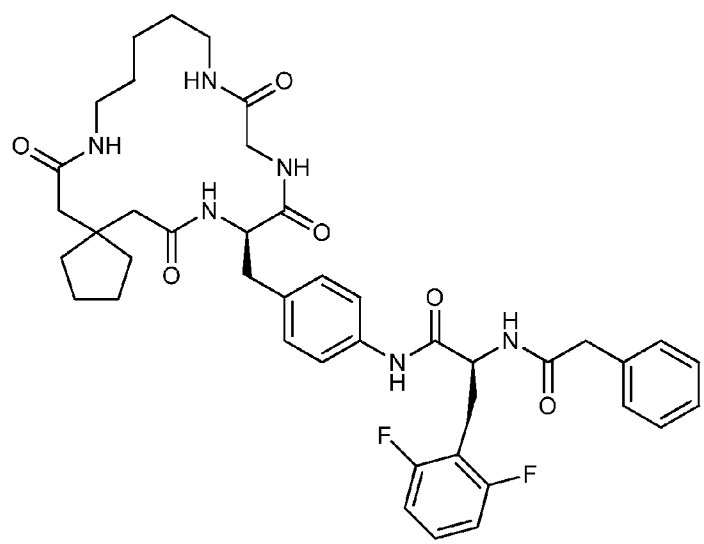
Compound No.	Structure
183	
184	

FIG. 12-35

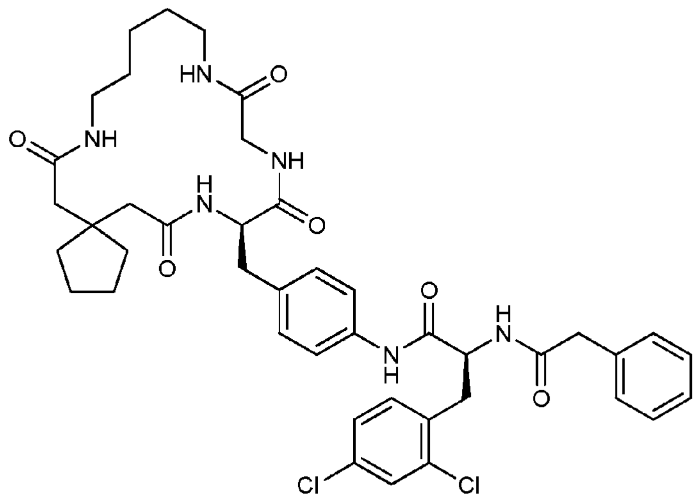
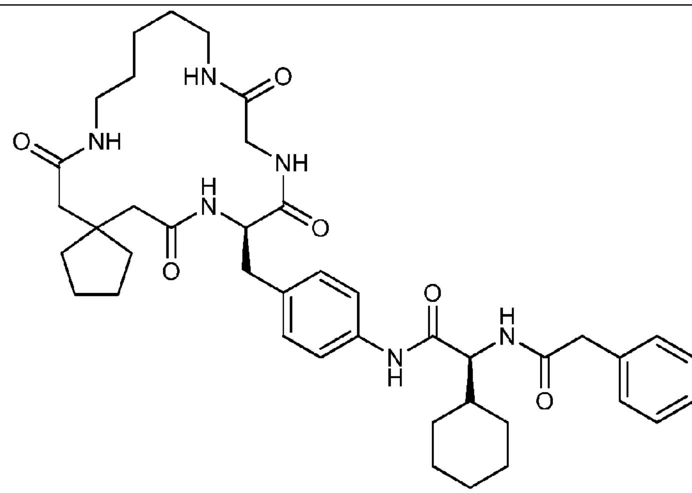
Compound No.	Structure
185	
186	

FIG. 12-36

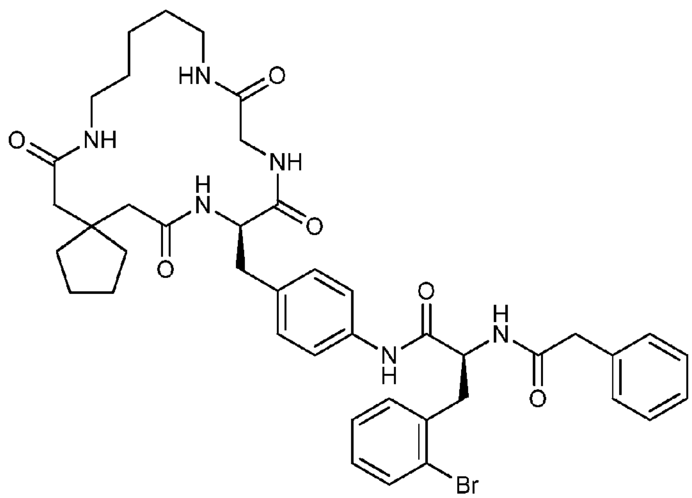
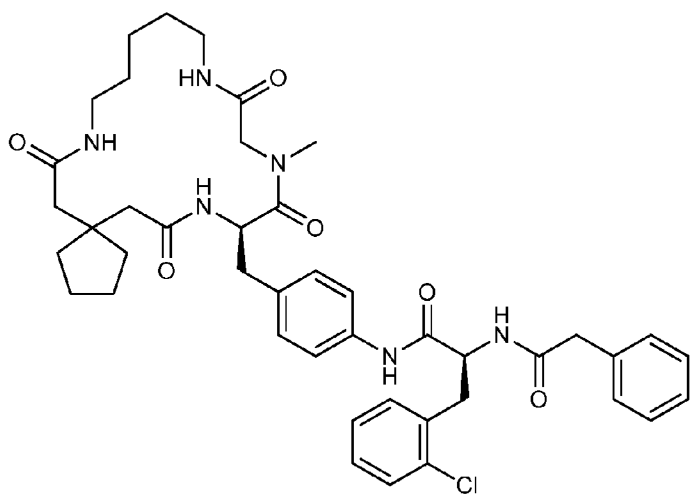
Compound No.	Structure
187	
188	

FIG. 12-37

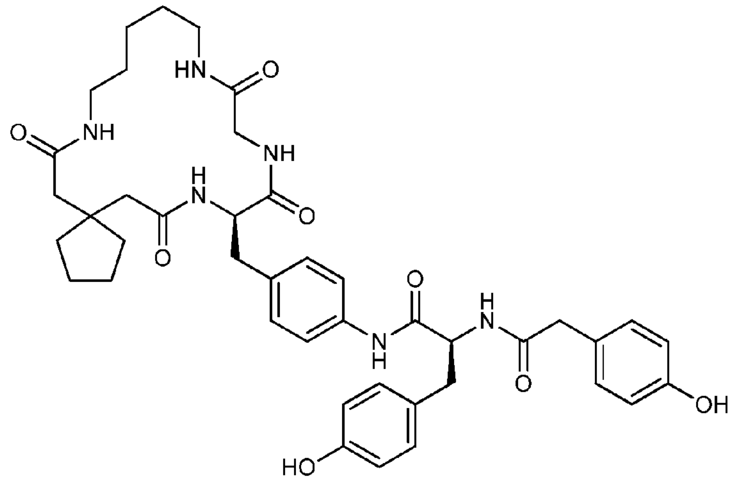
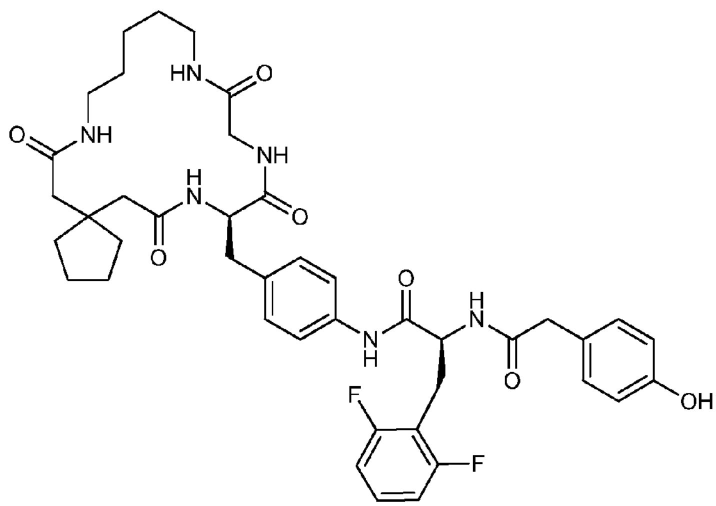
Compound No.	Structure
189	
190	

FIG. 12-38

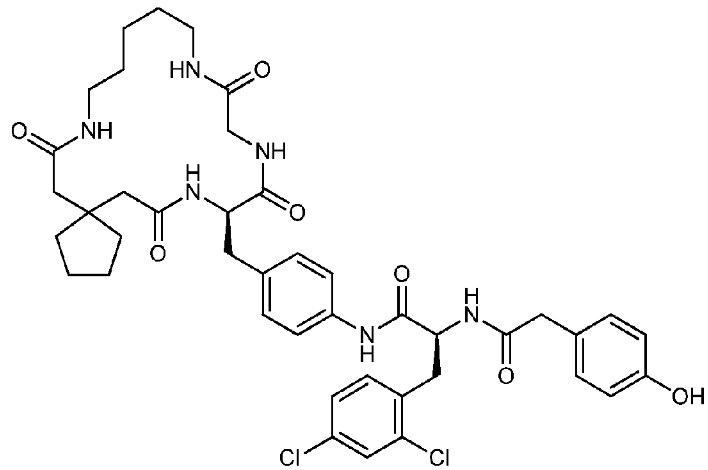
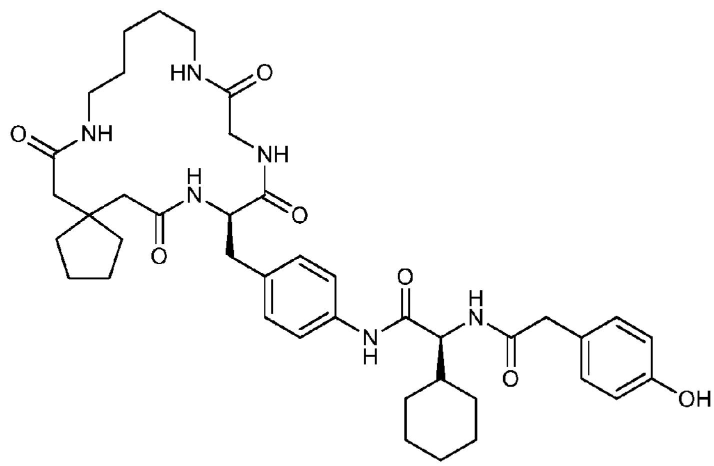
Compound No.	Structure
191	
192	

FIG. 12-39

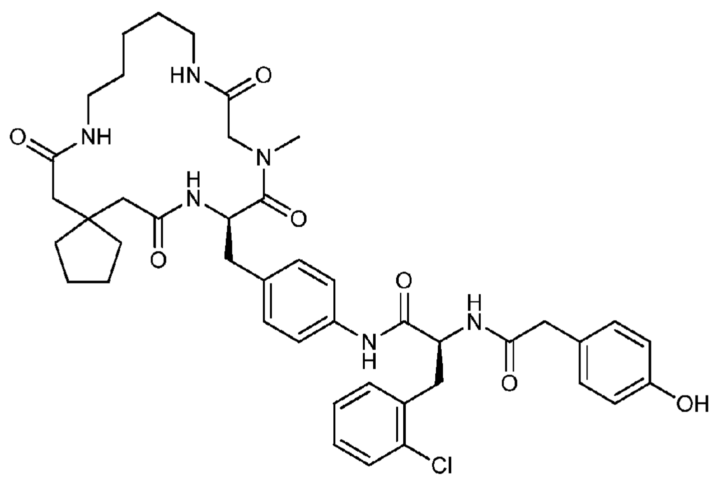
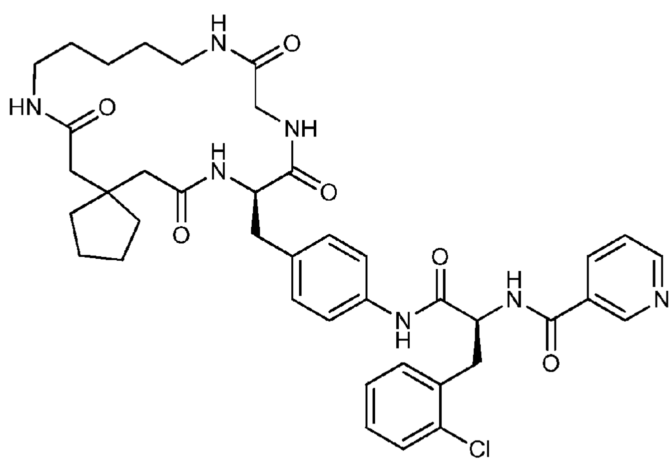
Compound No.	Structure
193	
194	

FIG. 12-40

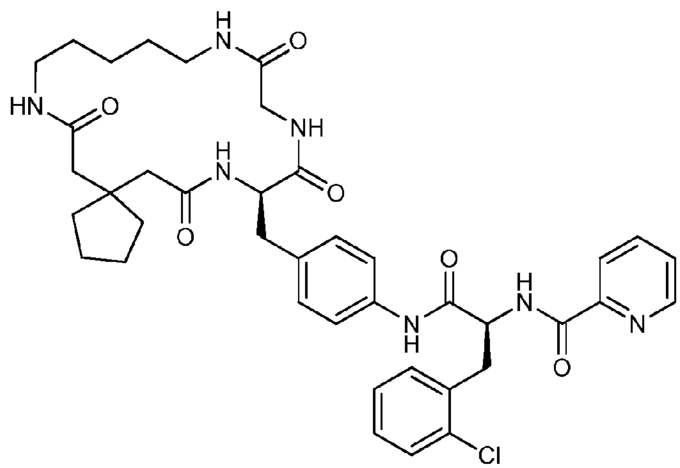
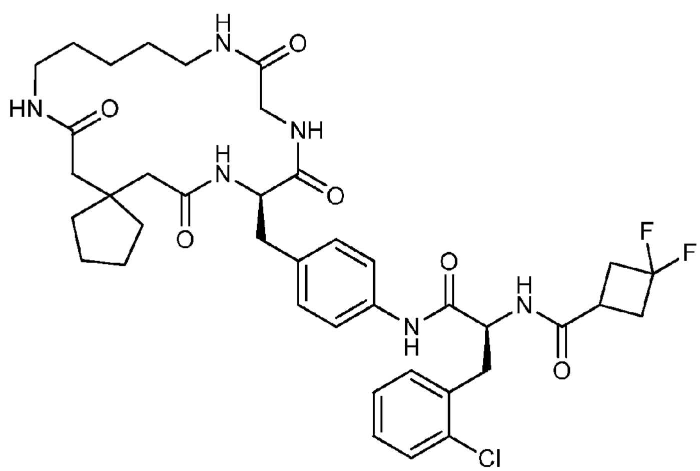
Compound No.	Structure
195	
196	

FIG. 12-41

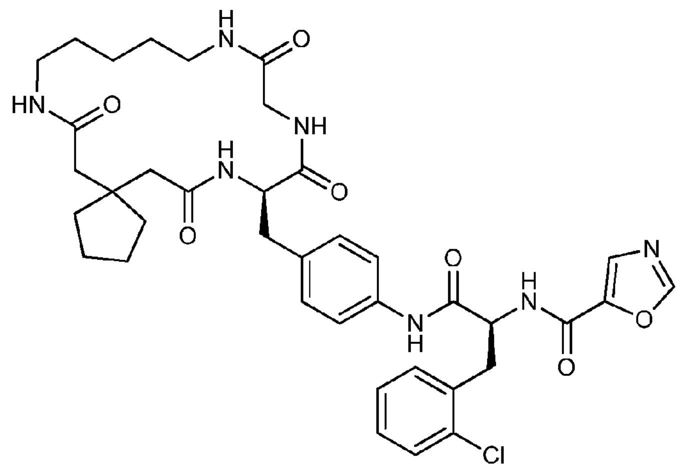
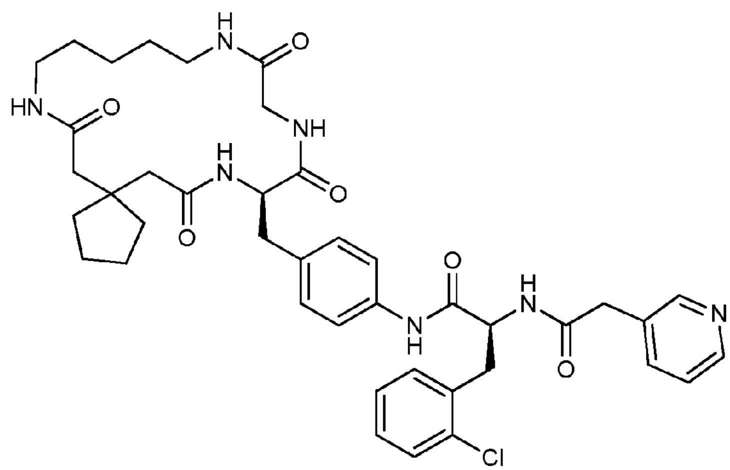
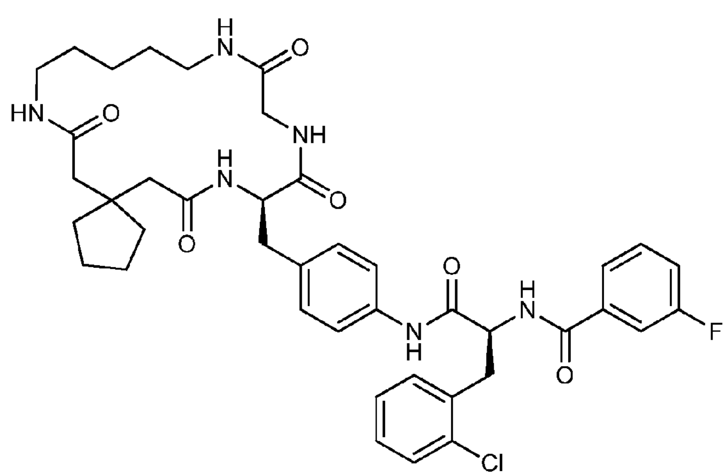
Compound No.	Structure
197	
198	
199	

FIG. 12-42

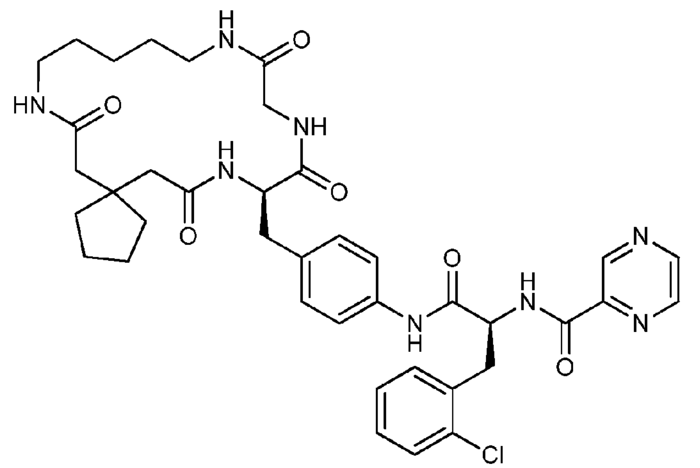
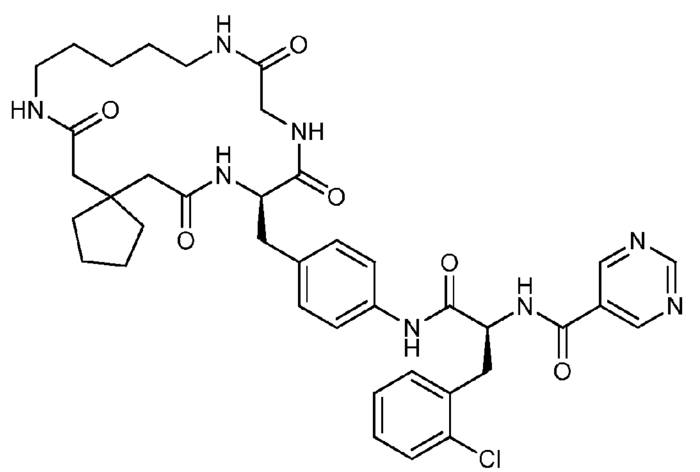
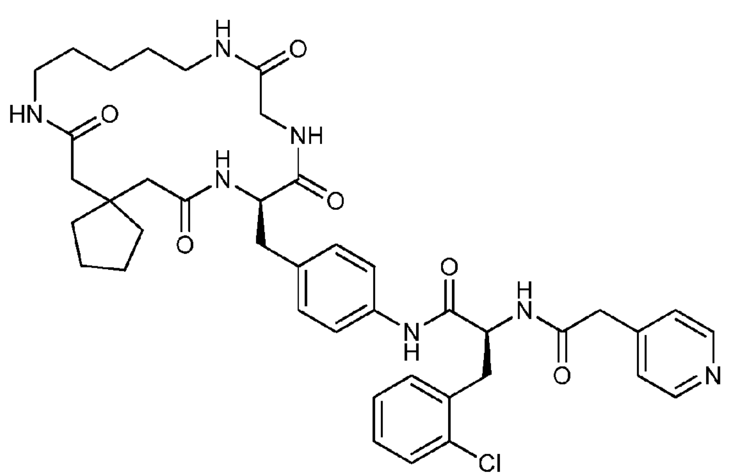
Compound No.	Structure
200	
201	
202	

FIG. 12-43

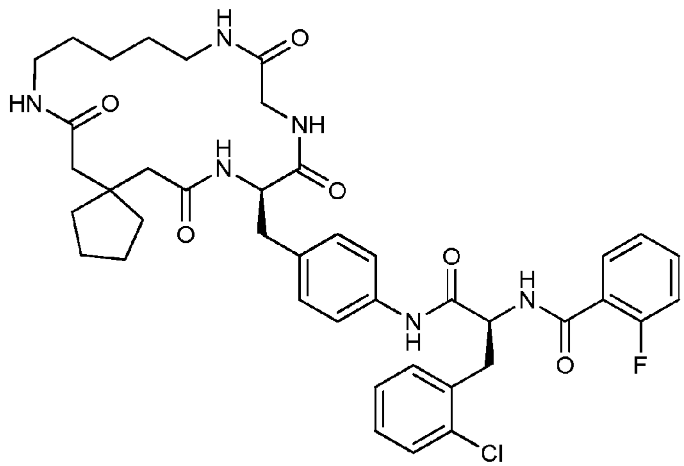
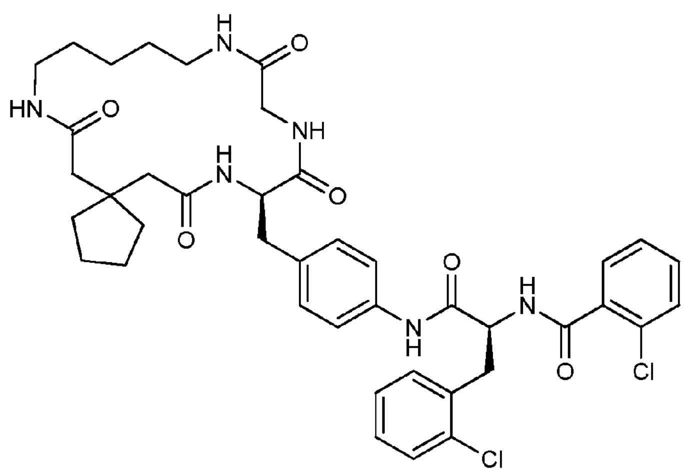
Compound No.	Structure
203	
204	

FIG. 12-44

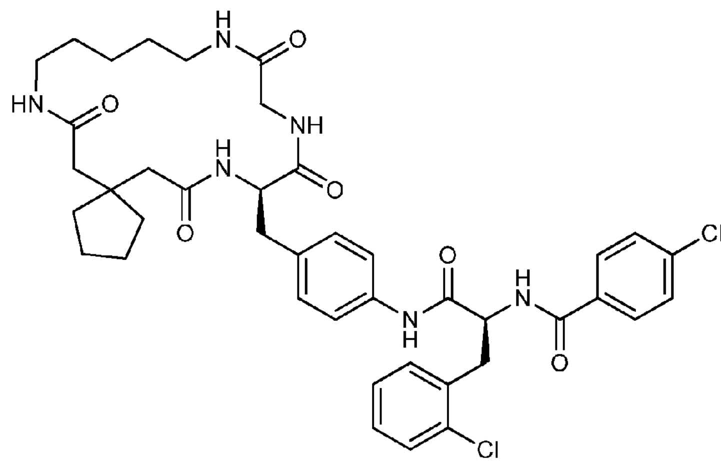
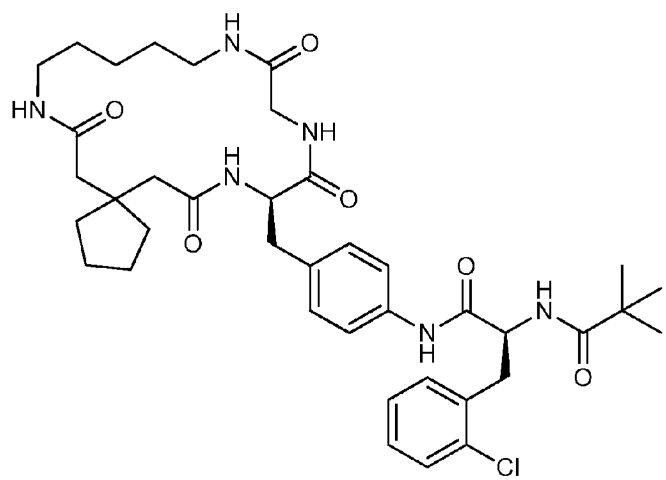
Compound No.	Structure
205	
206	

FIG. 12-45

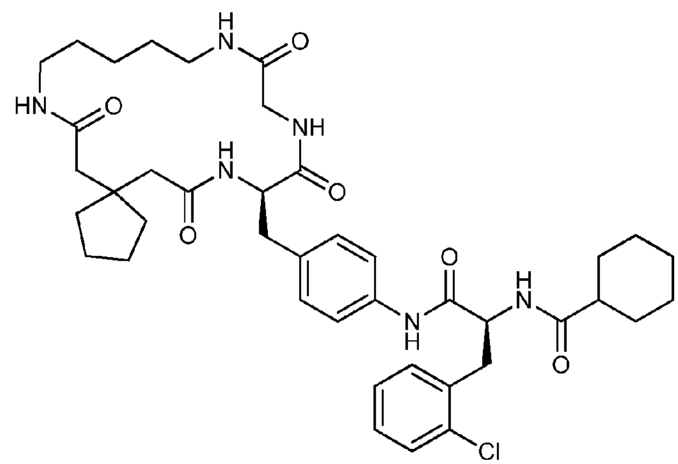
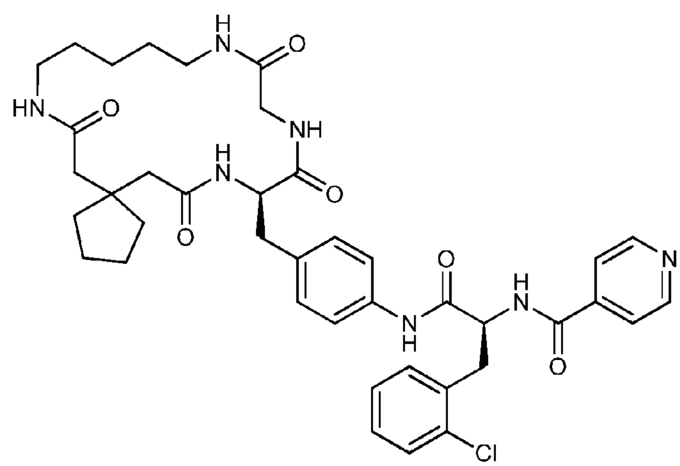
Compound No.	Structure
207	
208	

FIG. 12-46

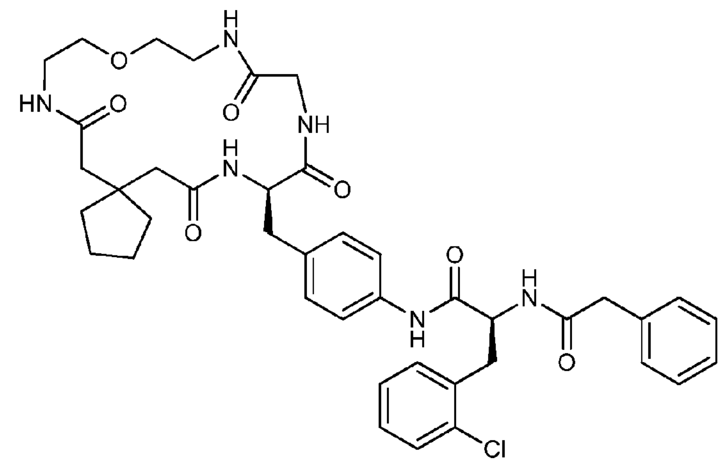
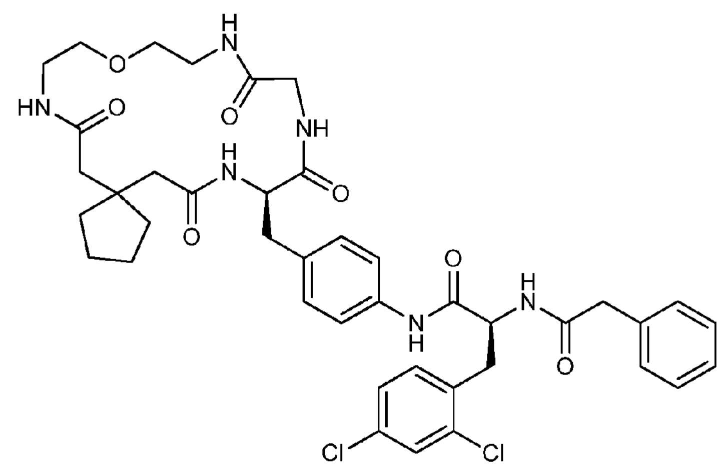
Compound No.	Structure
209	
210	

FIG. 12-47

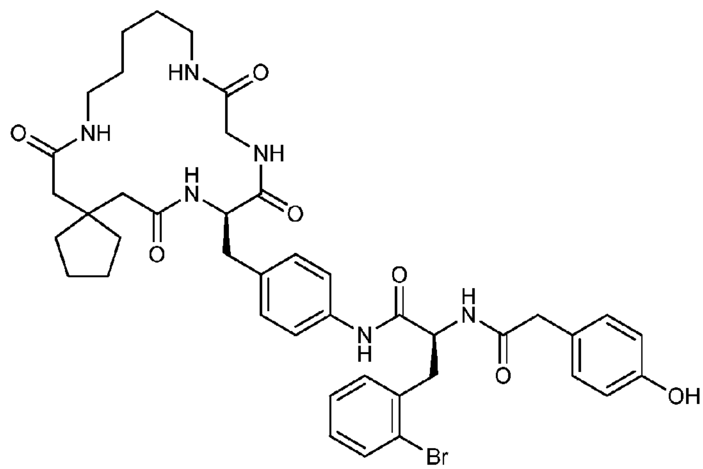
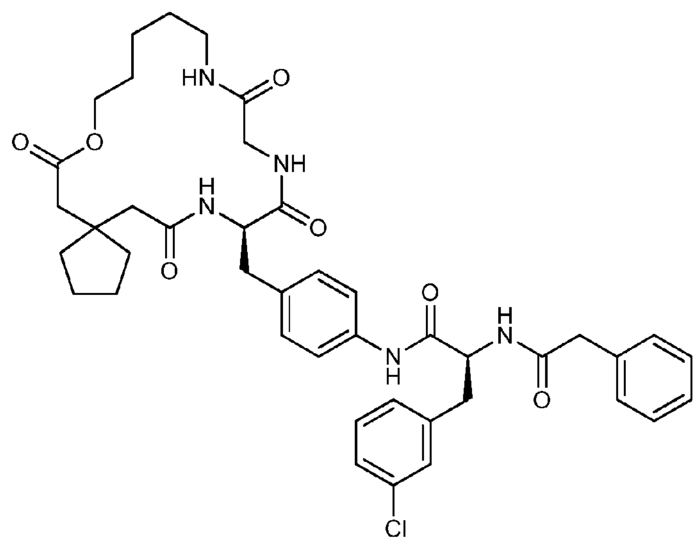
Compound No.	Structure
211	
212	

FIG. 12-48

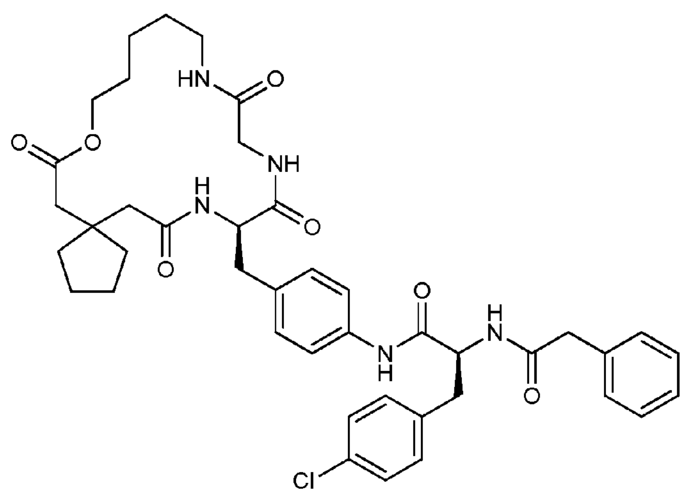
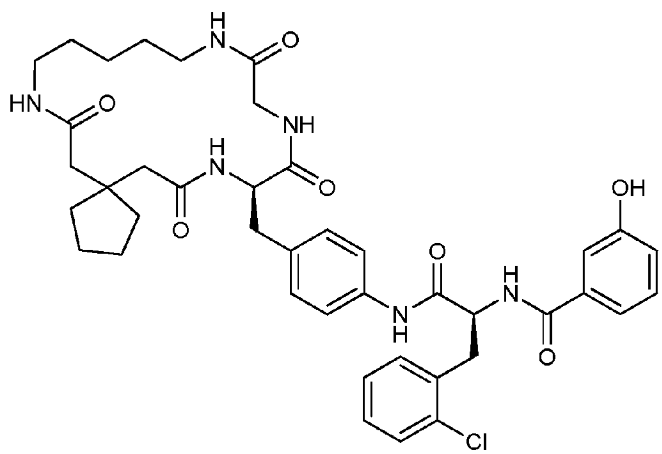
Compound No.	Structure
213	
214	

FIG. 12-49

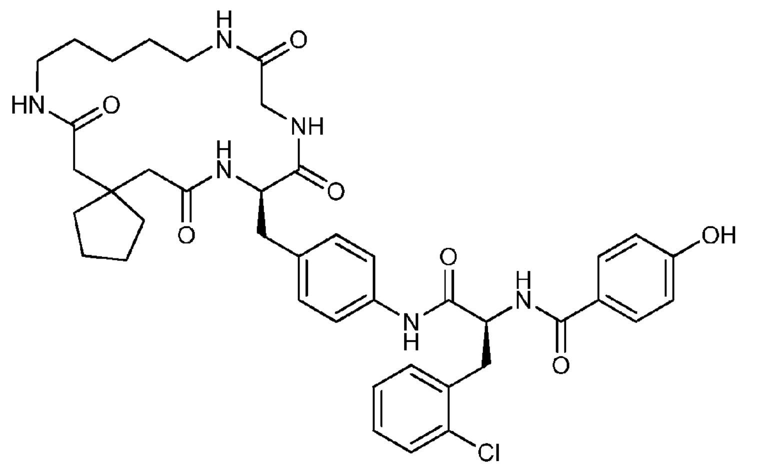
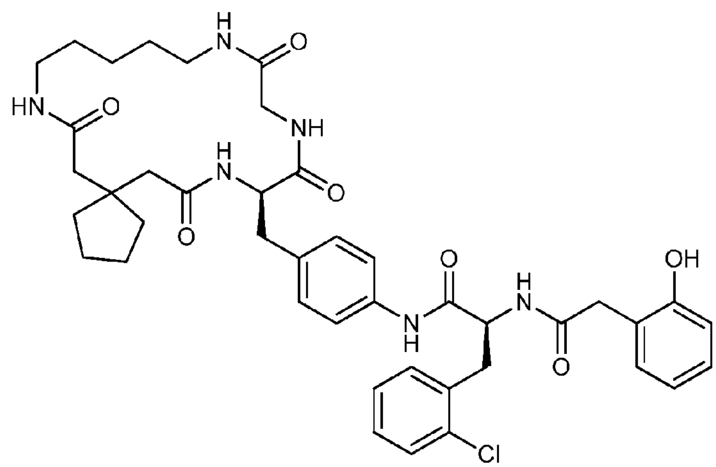
Compound No.	Structure
215	
216	

FIG. 12-50

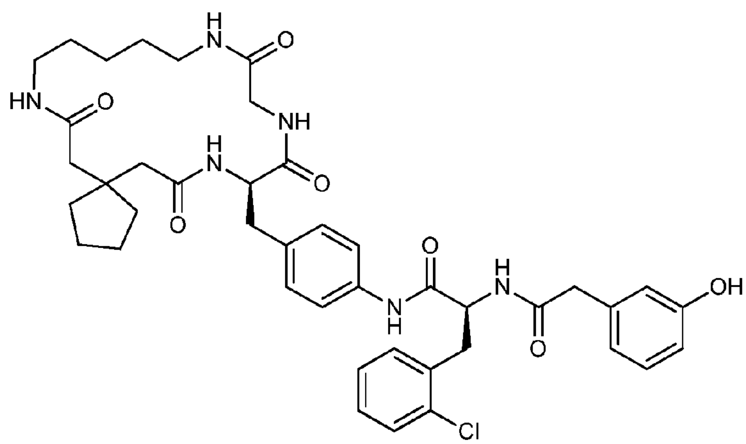
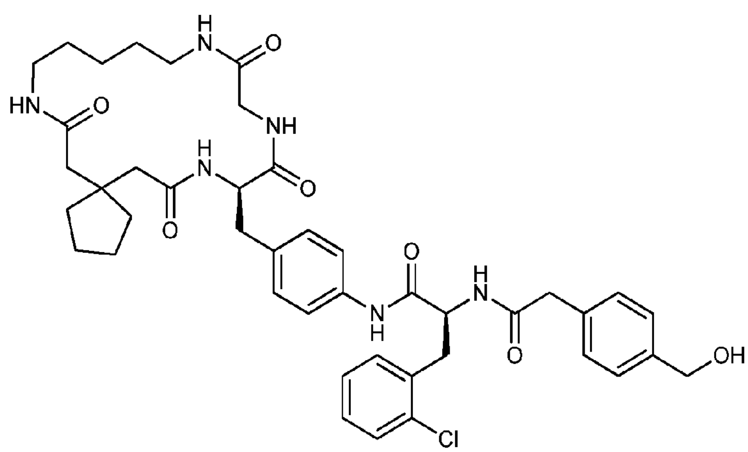
Compound No.	Structure
217	
218	

FIG. 12-51

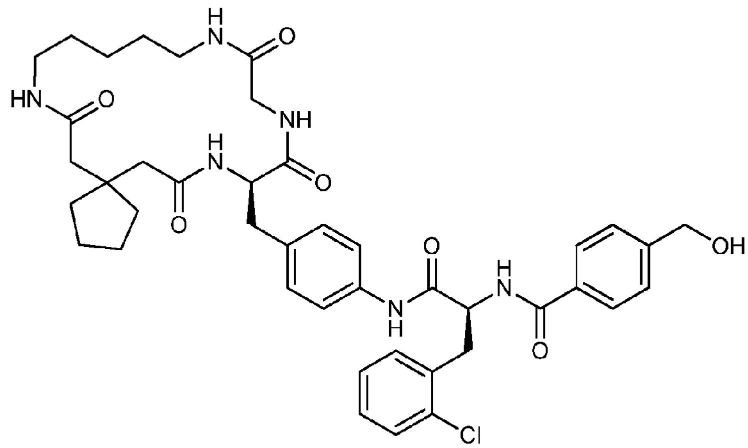
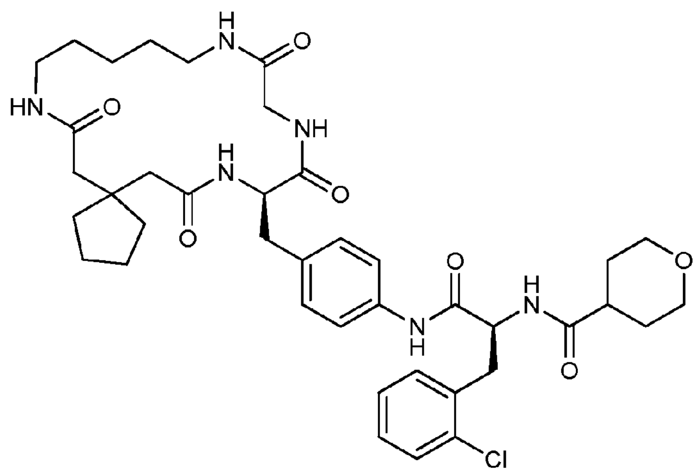
Compound No.	Structure
219	
220	

FIG. 12-52

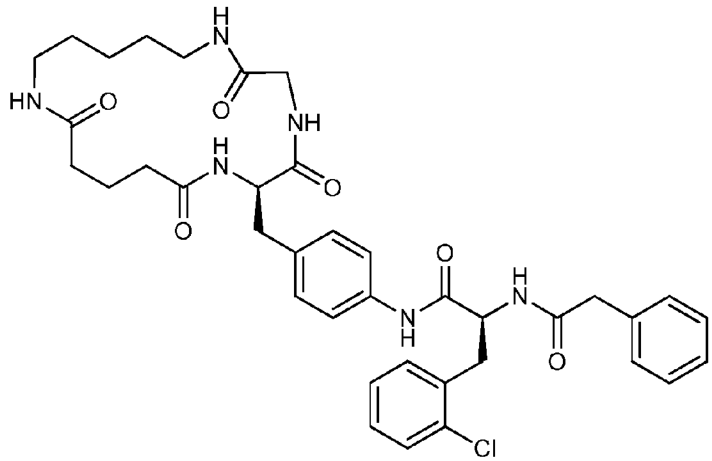
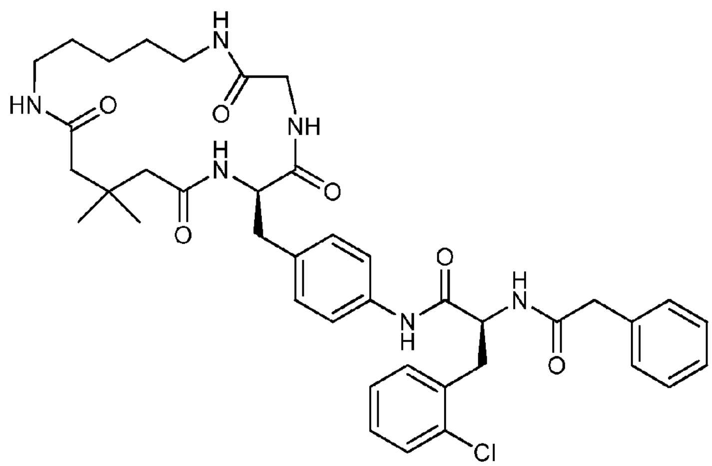
Compound No.	Structure
221	
222	

FIG. 12-53

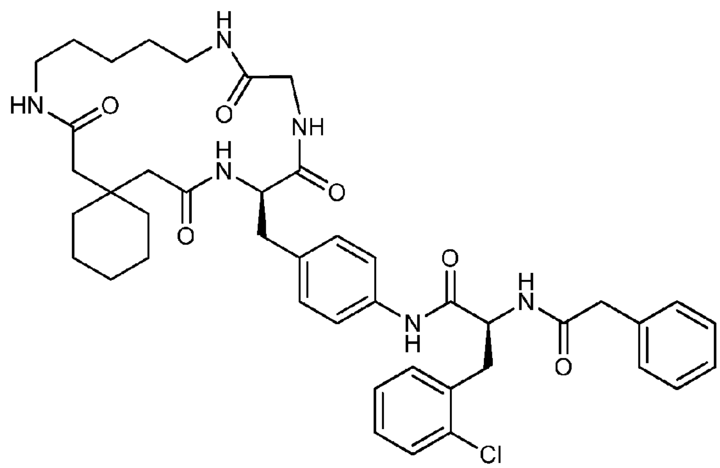
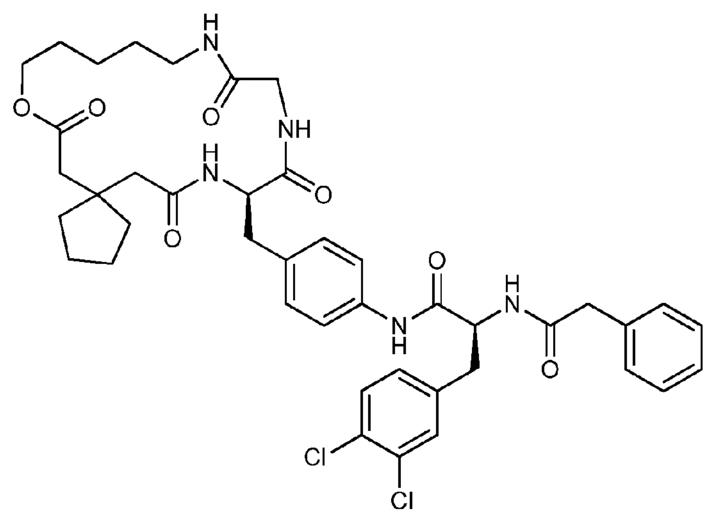
Compound No.	Structure
223	
224	

FIG. 12-54

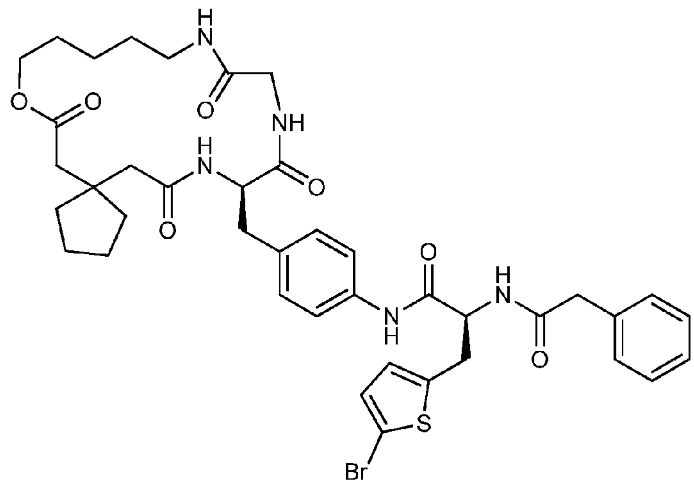
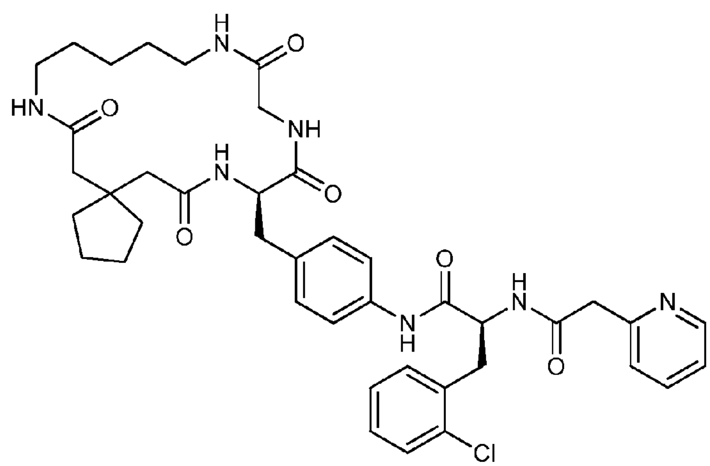
Compound No.	Structure
225	
226	

FIG. 12-55

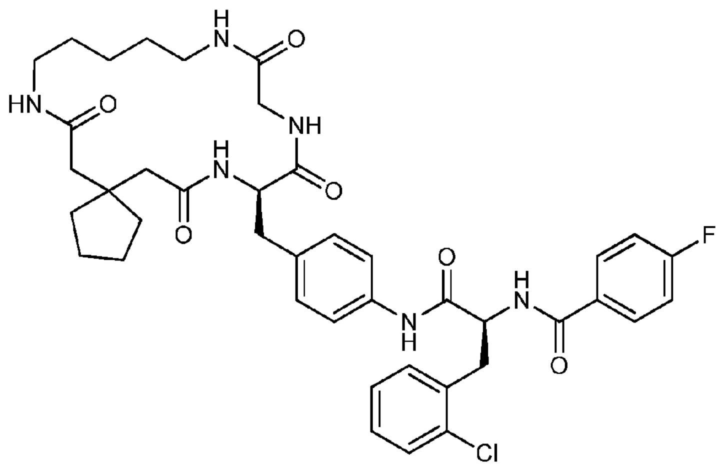
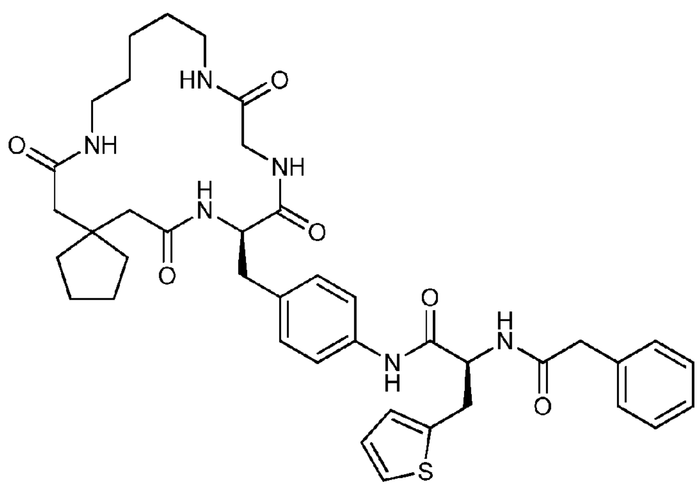
Compound No.	Structure
227	
228	

FIG. 12-56

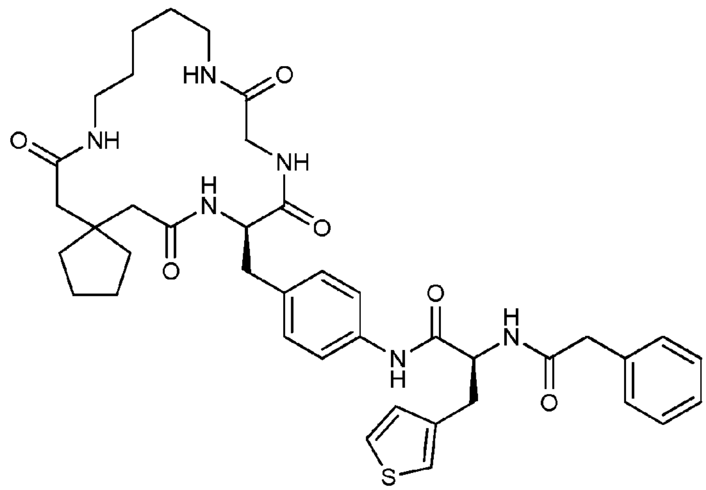
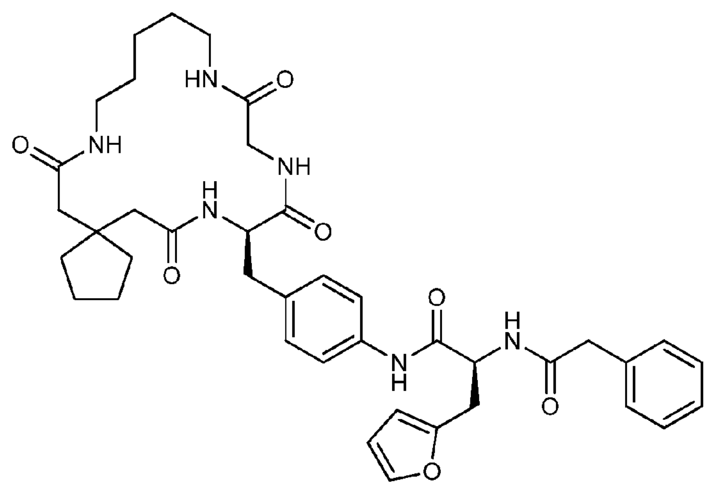
Compound No.	Structure
229	
230	

FIG. 12-57

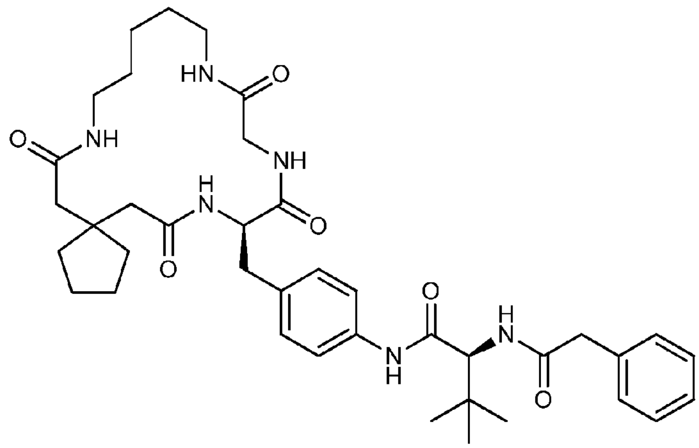
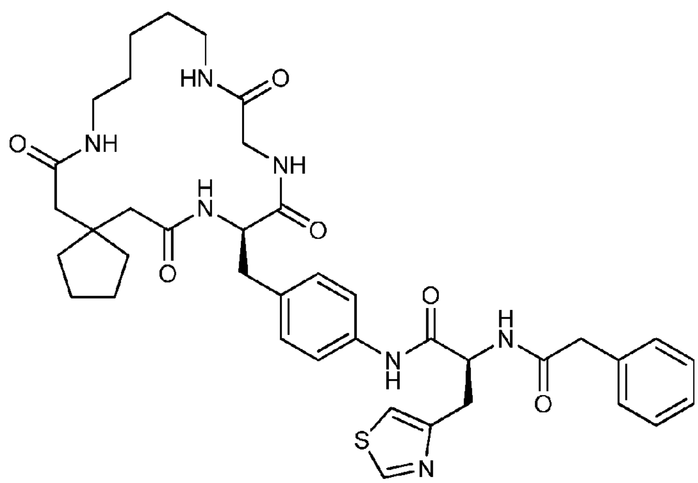
Compound No.	Structure
231	
232	

FIG. 12-58

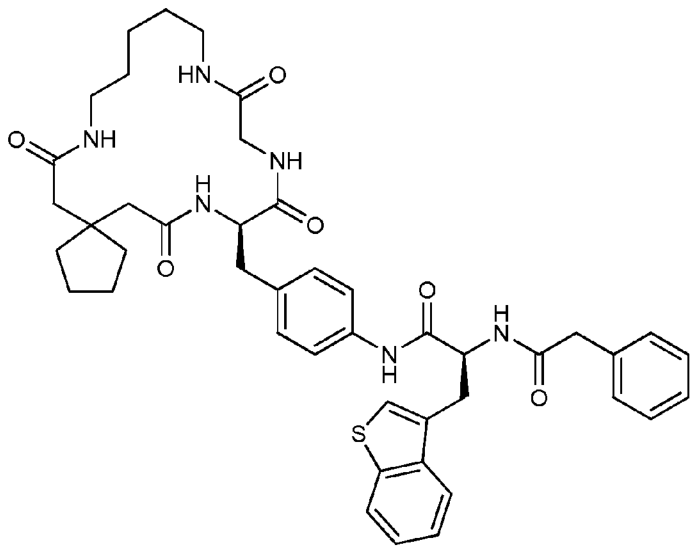
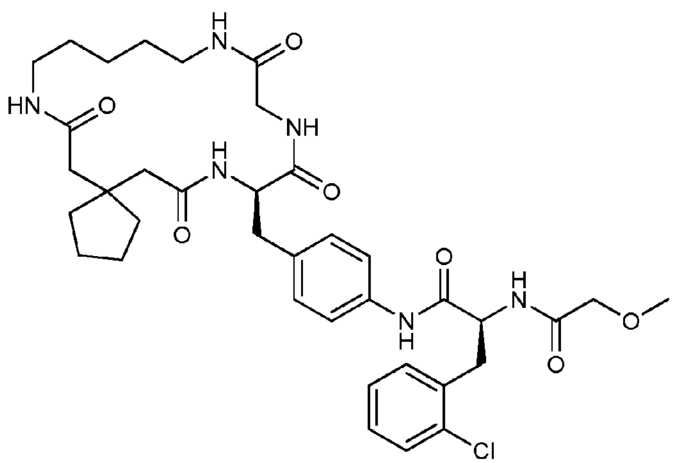
Compound No.	Structure
233	
234	

FIG. 12-59

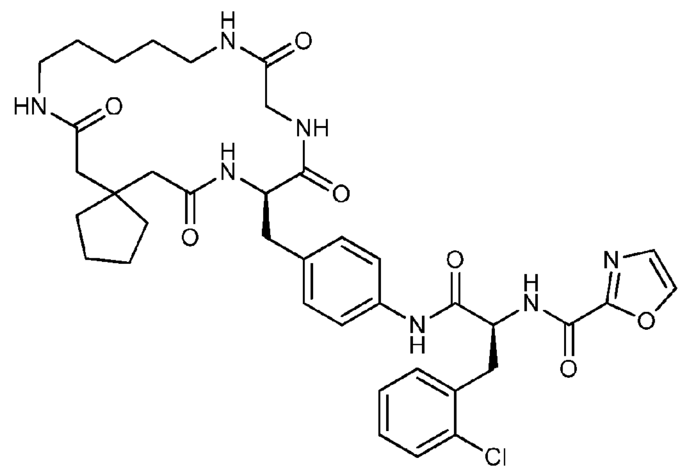
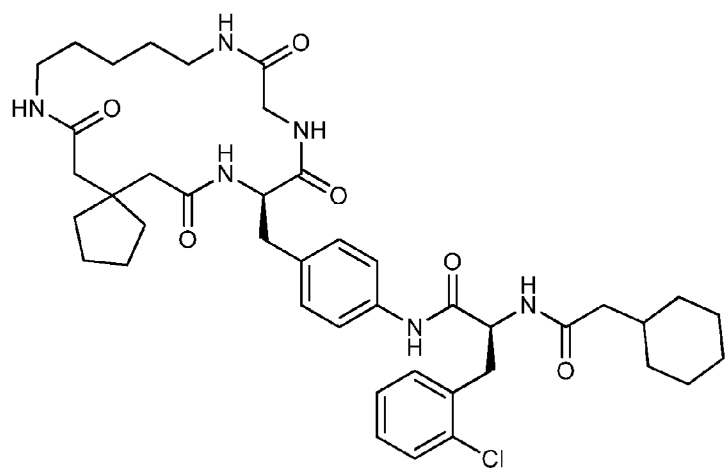
Compound No.	Structure
235	
236	

FIG. 12-60

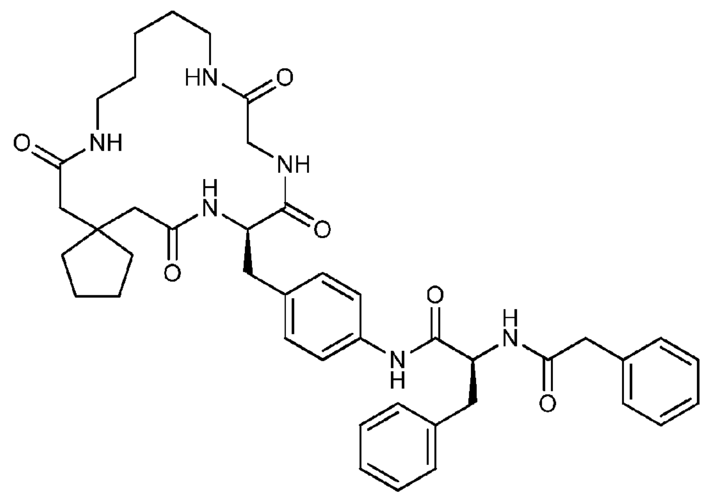
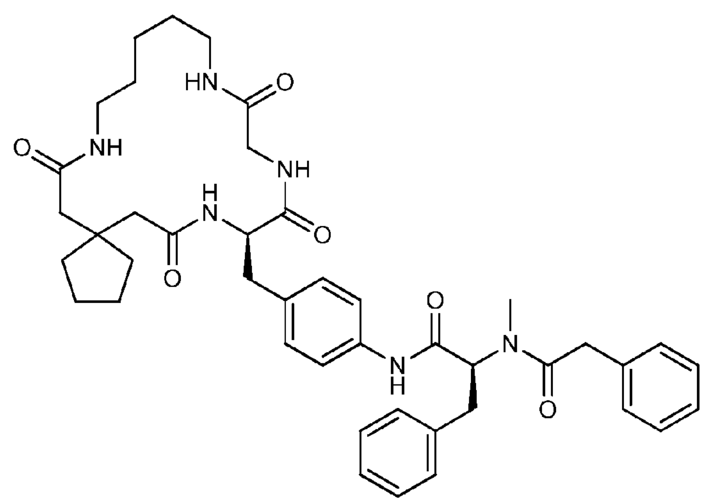
Compound No.	Structure
237	
238	

FIG. 12-61

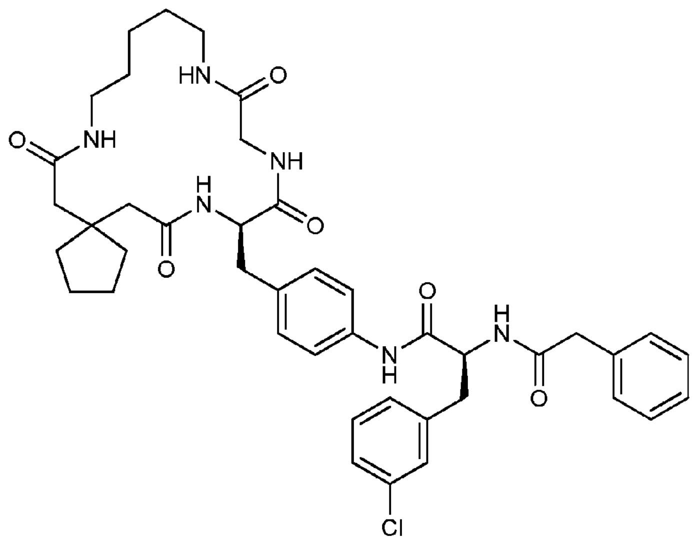
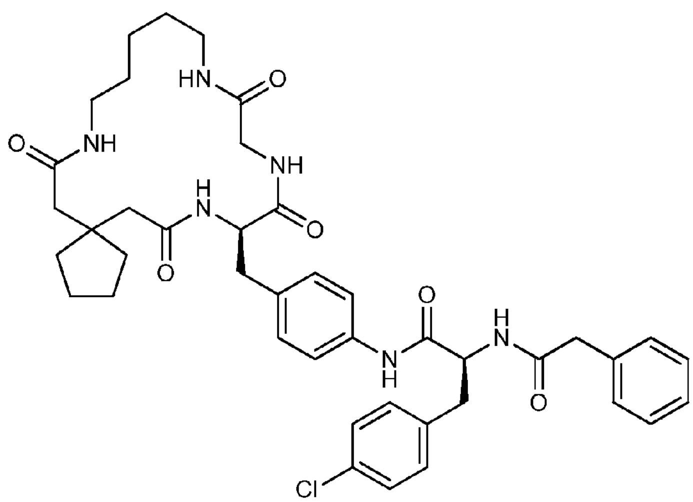
Compound No.	Structure
239	
240	

FIG. 12-62

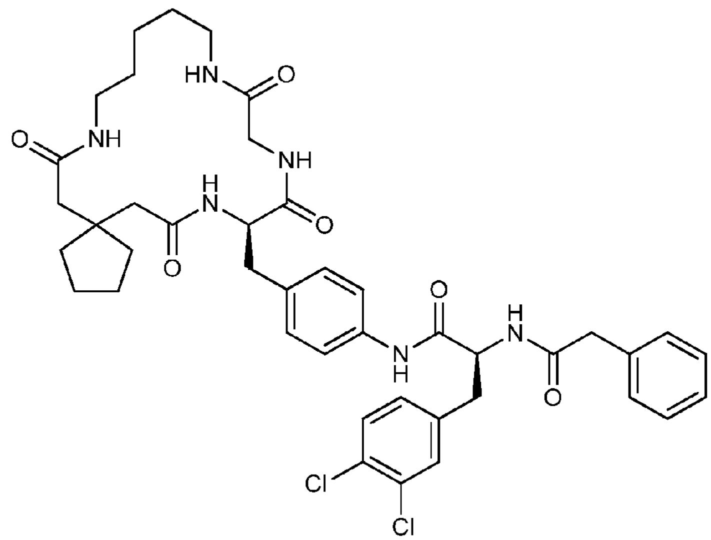
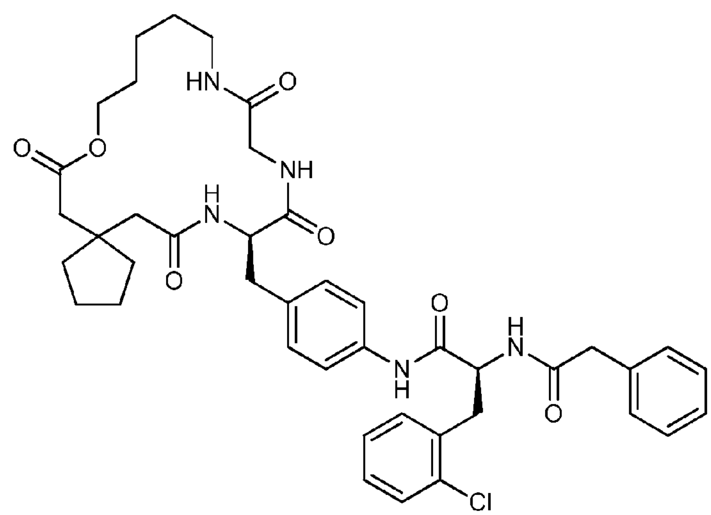
Compound No.	Structure
241	
242	

FIG. 12-63

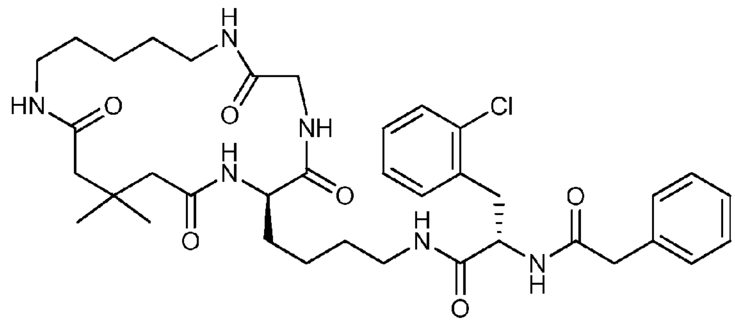
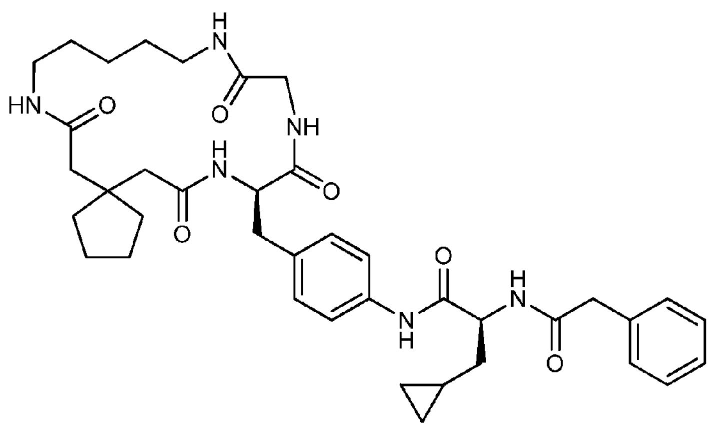
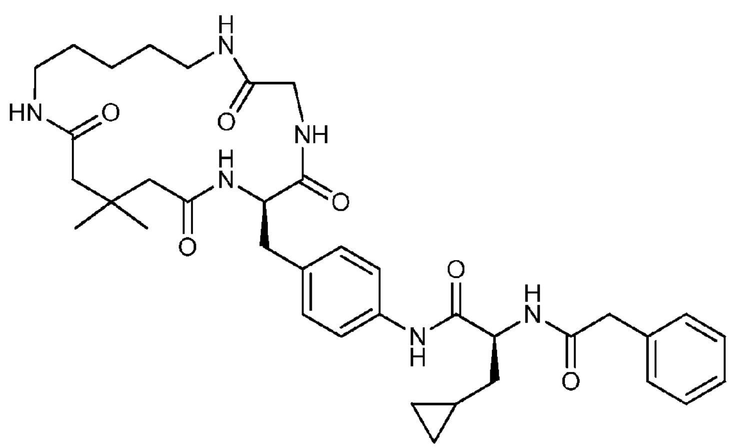
Compound No.	Structure
243	
244	
245	

FIG. 12-64

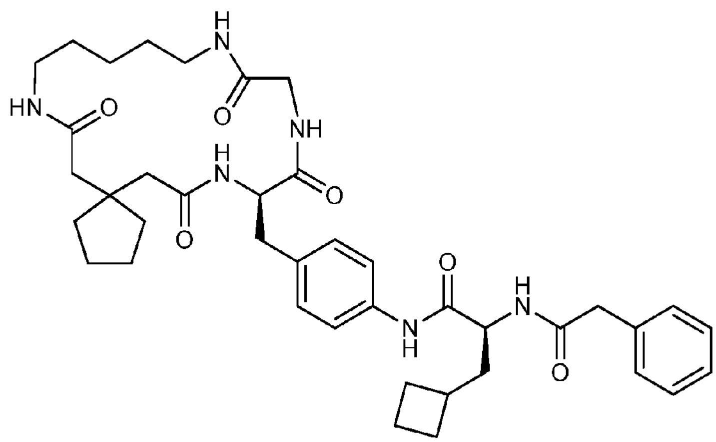
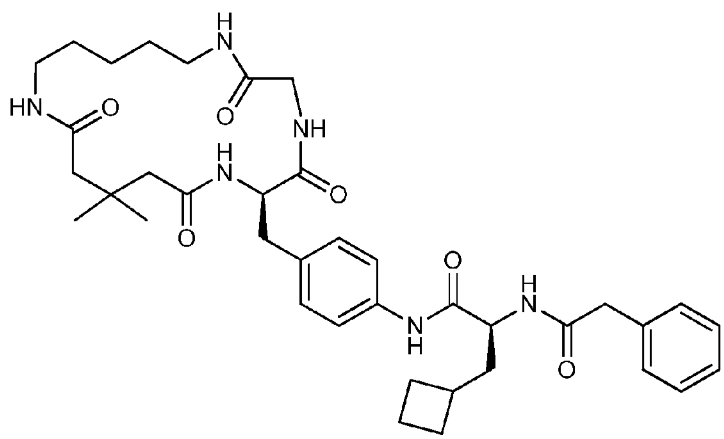
Compound No.	Structure
246	
247	

FIG. 12-65

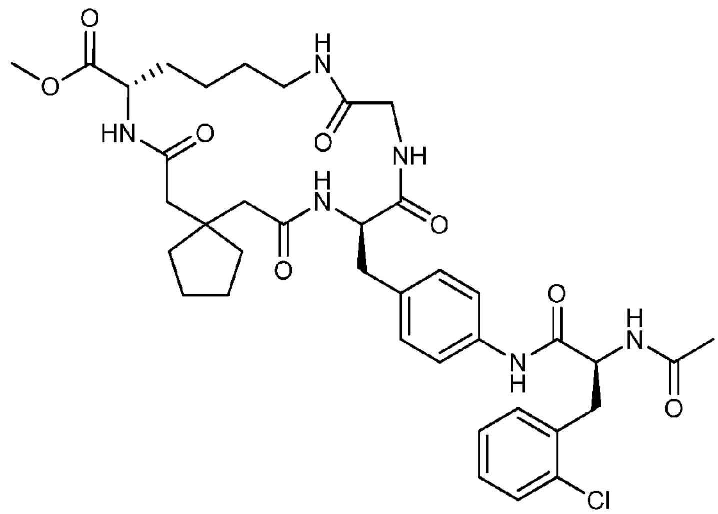
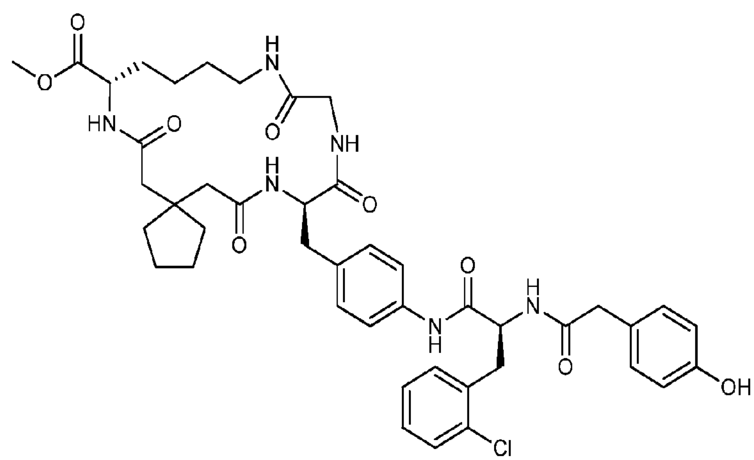
Compound No.	Structure
248	
249	

FIG. 12-66

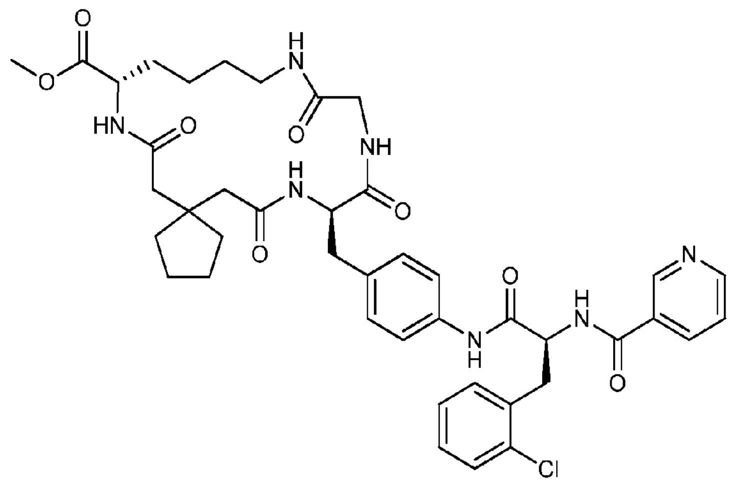
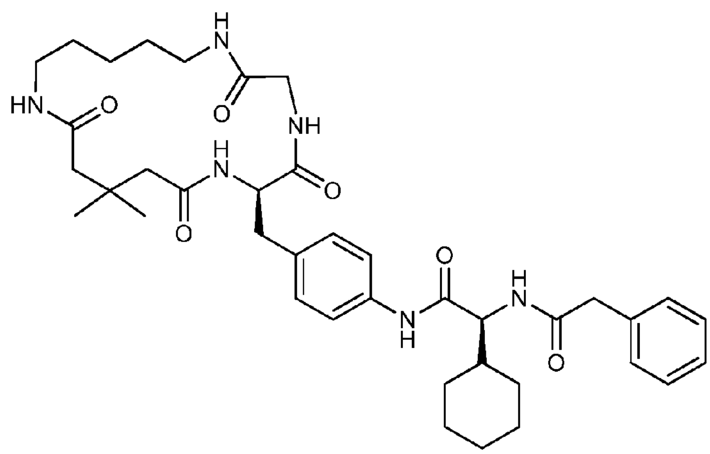
Compound No.	Structure
250	
251	

FIG. 12-67

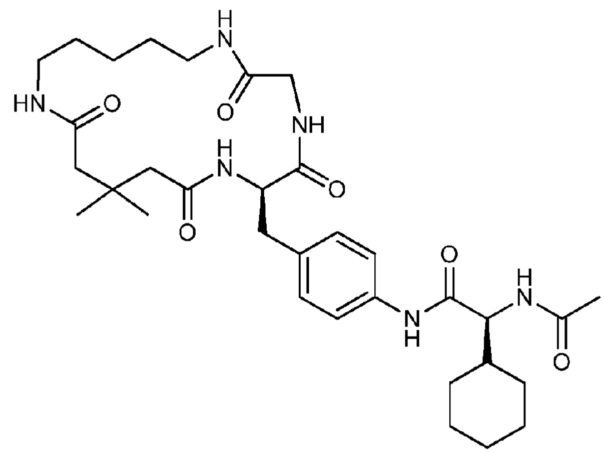
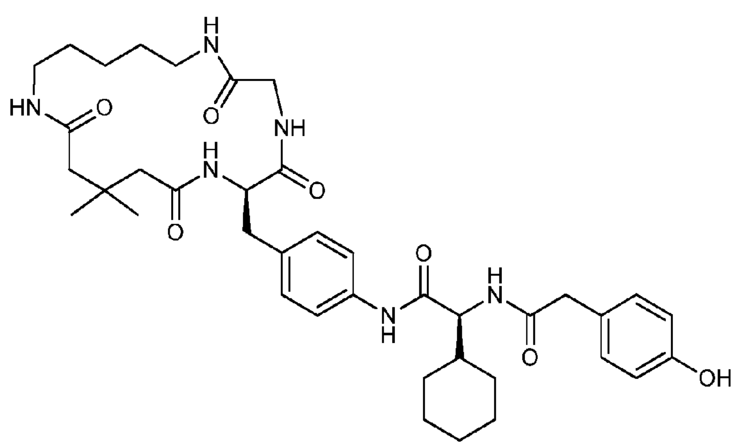
Compound No.	Structure
252	
253	

FIG. 12-68

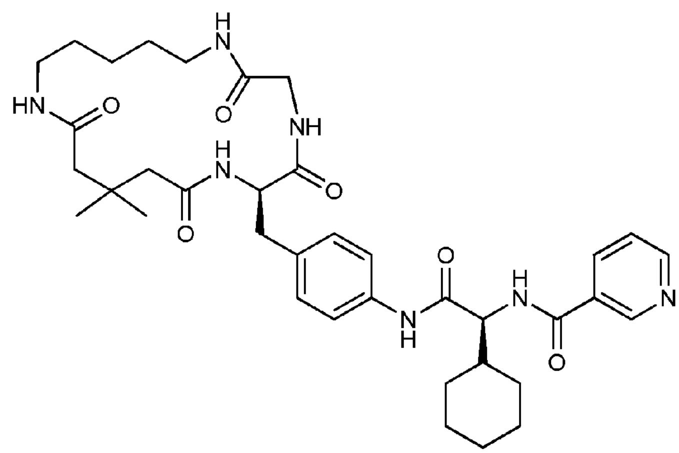
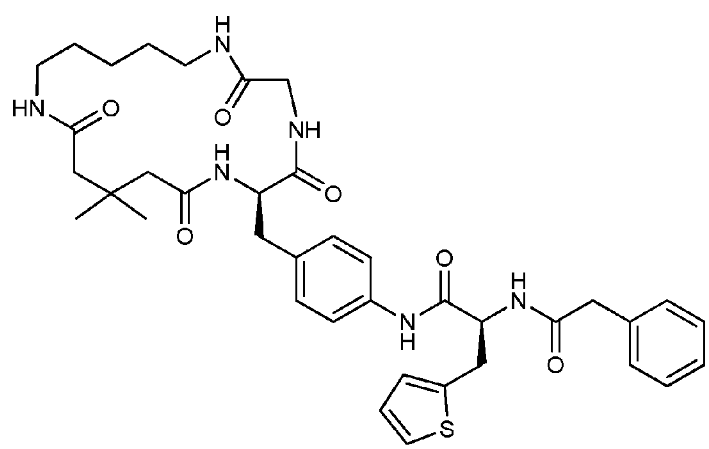
Compound No.	Structure
254	
255	

FIG. 12-69

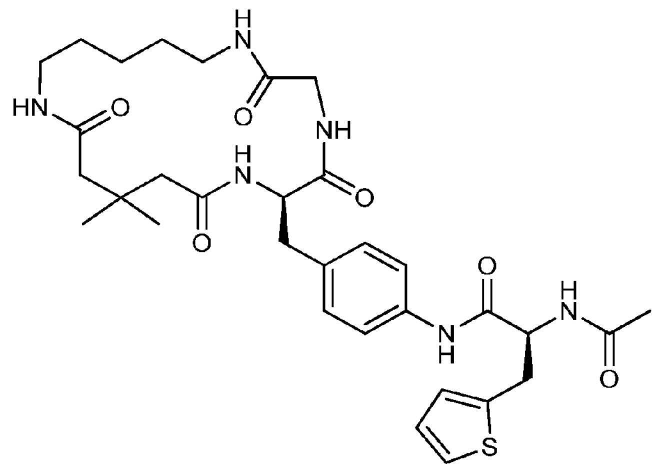
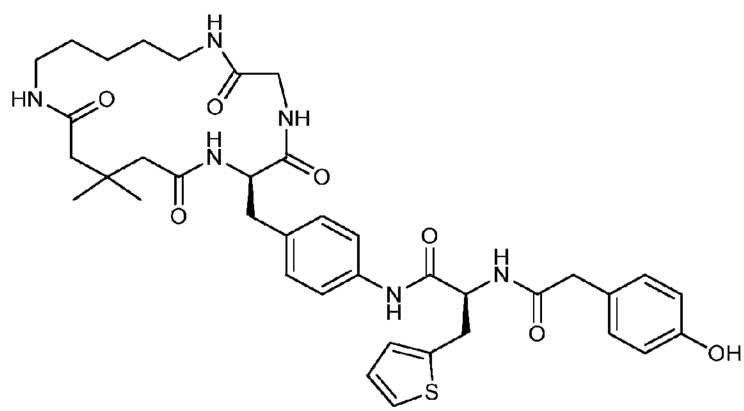
Compound No.	Structure
256	
257	

FIG. 12-70

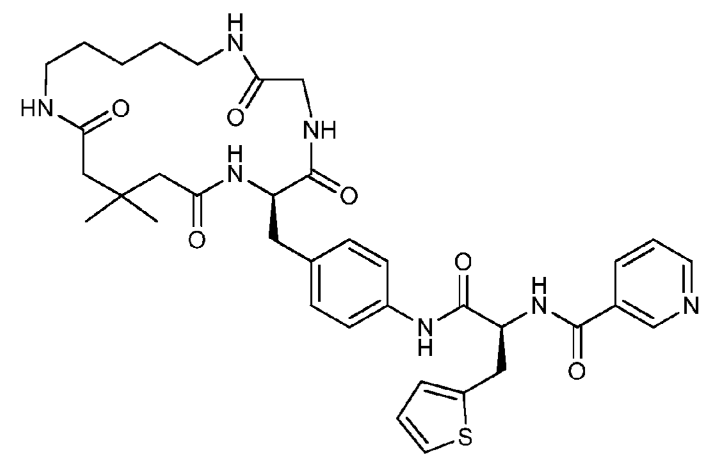
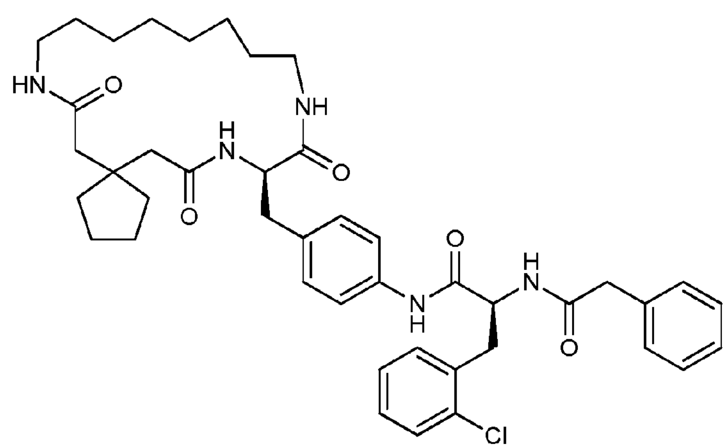
Compound No.	Structure
258	
259	

FIG. 12-71

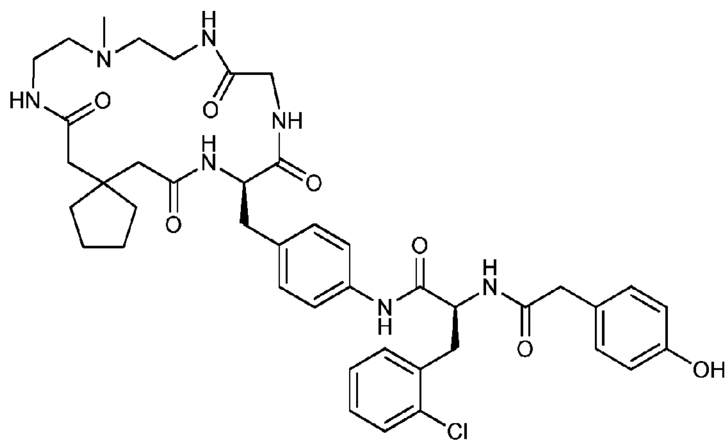
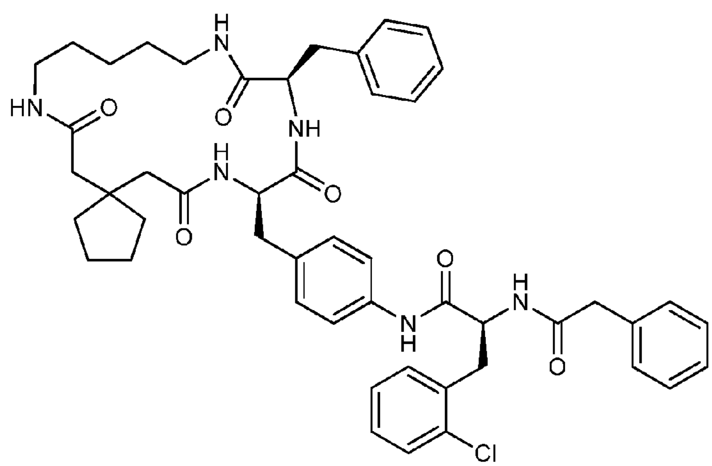
Compound No.	Structure
260	
261	

FIG. 12-72

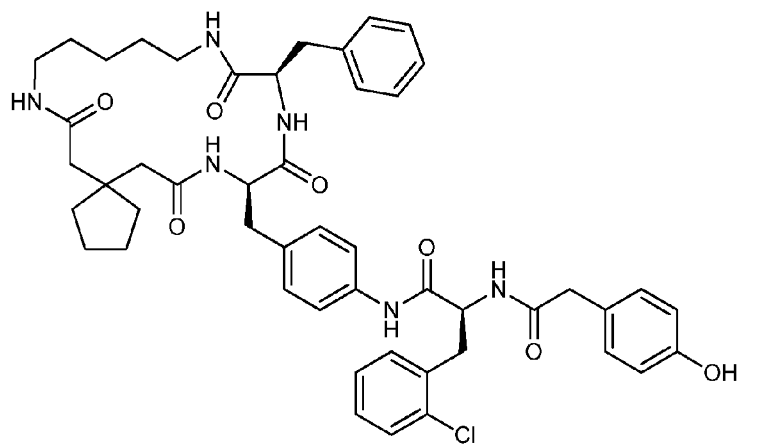
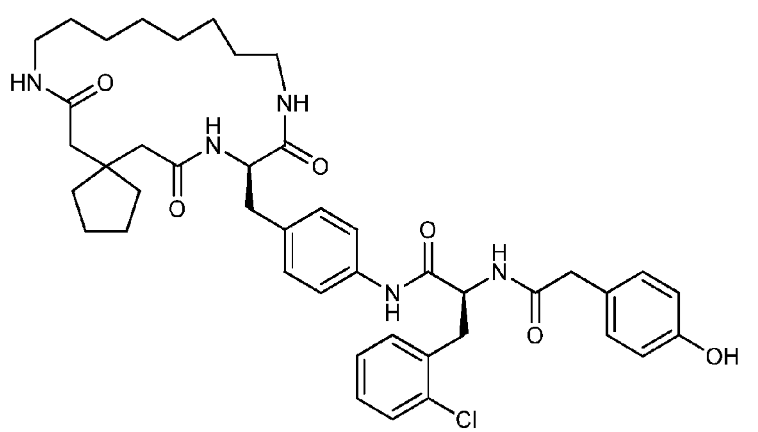
Compound No.	Structure
262	
263	

FIG. 12-73

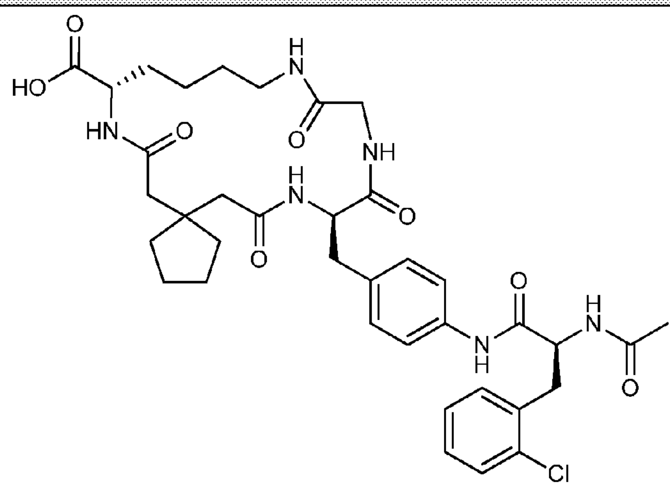
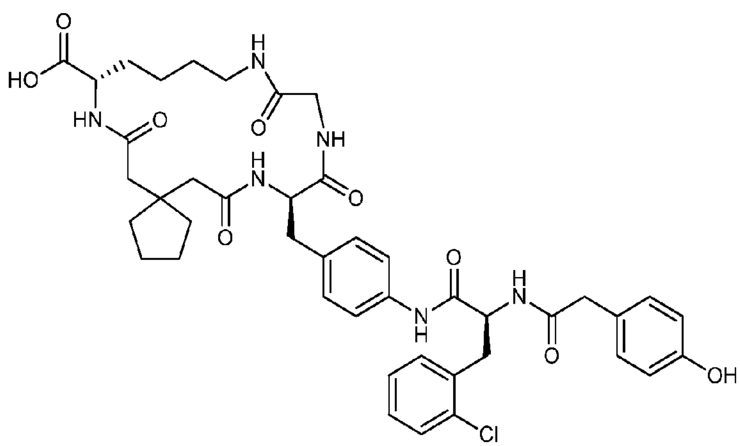
Compound No.	Structure
264	
265	

FIG. 12-74

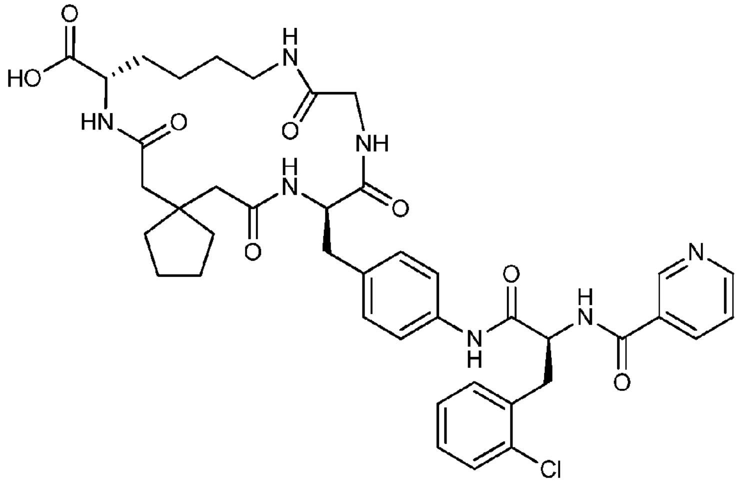
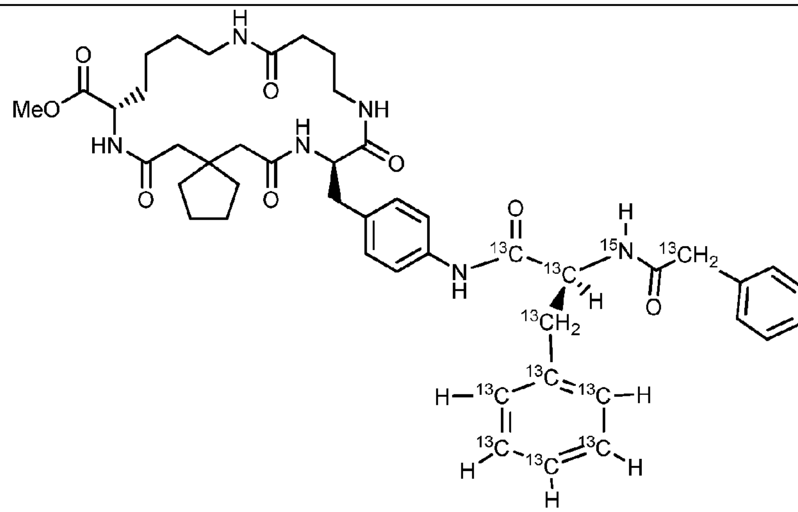
Compound No.	Structure
266	
267	

FIG. 12-75

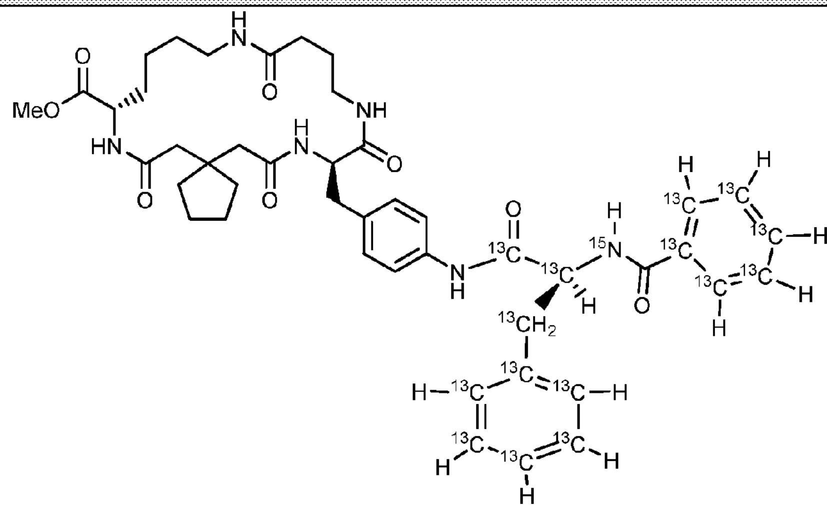
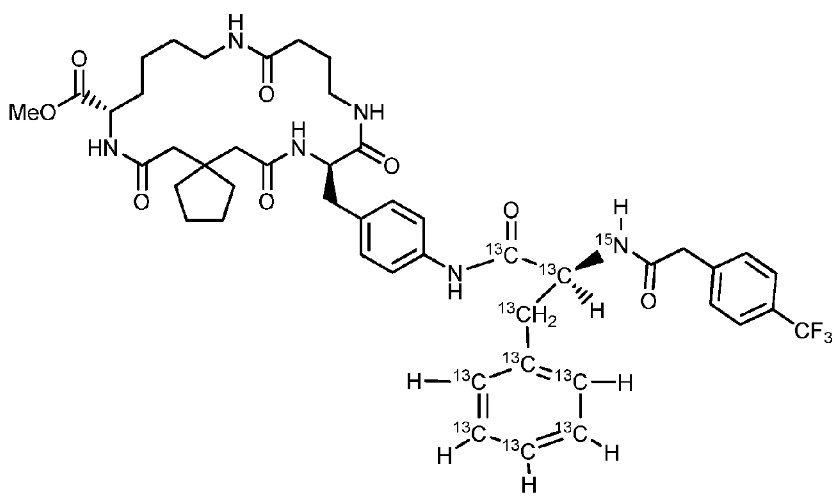
Compound No.	Structure
268	
269	

FIG. 12-76

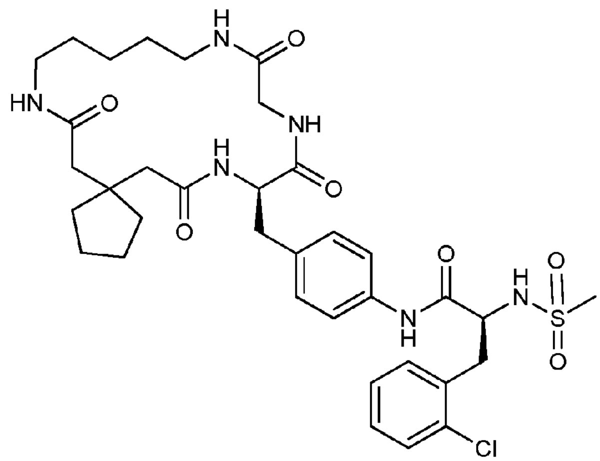
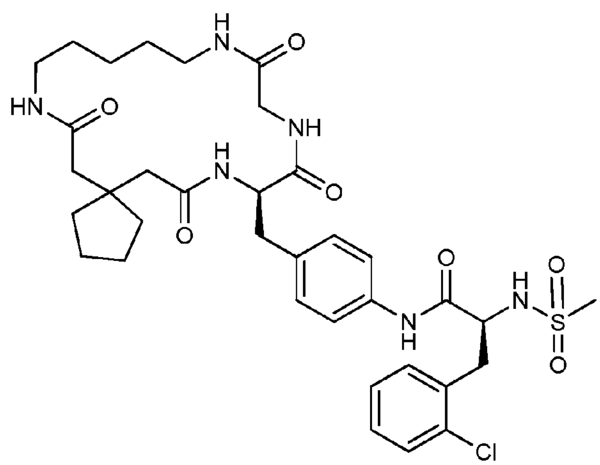
Compound No.	Structure
270	
270	

FIG. 12-77

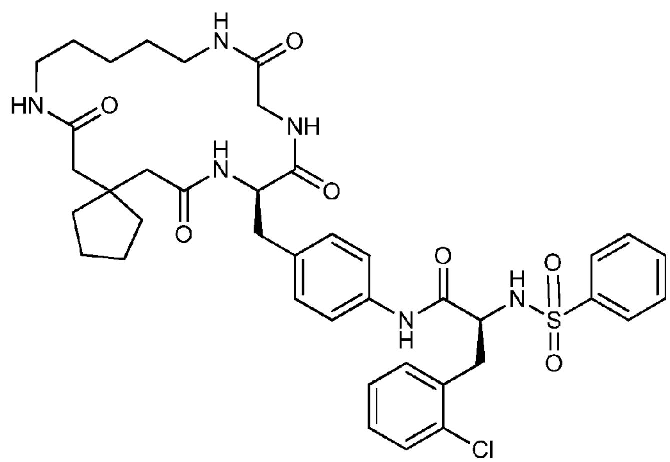
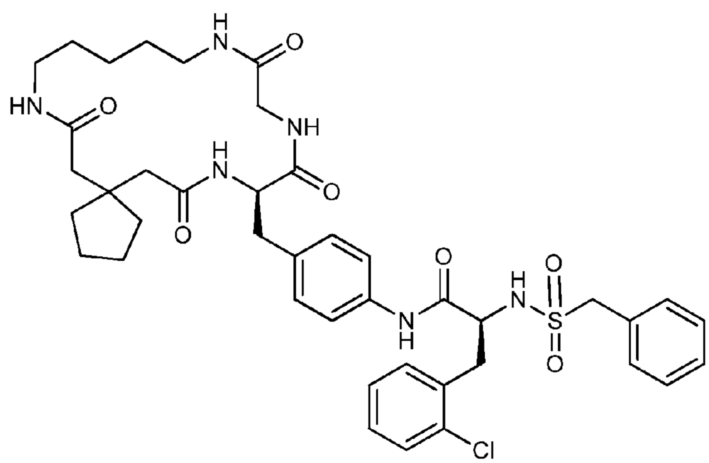
Compound No.	Structure
271	
272	

FIG. 12-78

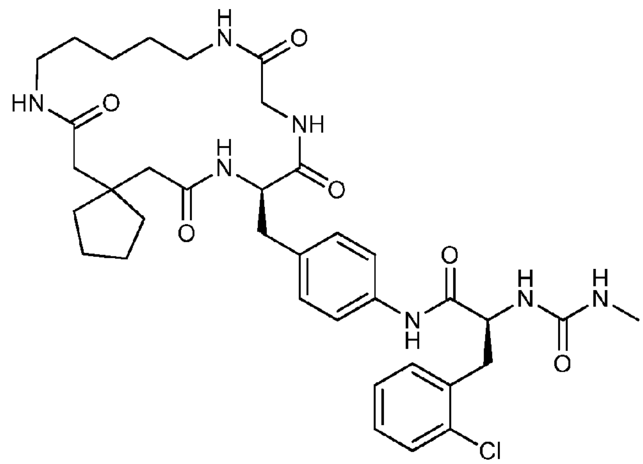
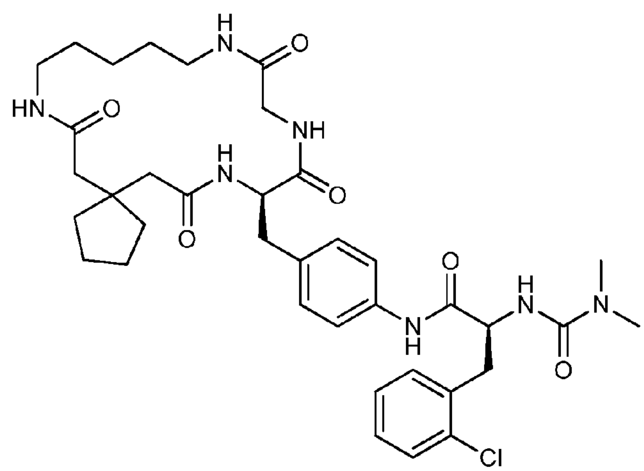
Compound No.	Structure
273	
274	

FIG. 12-79

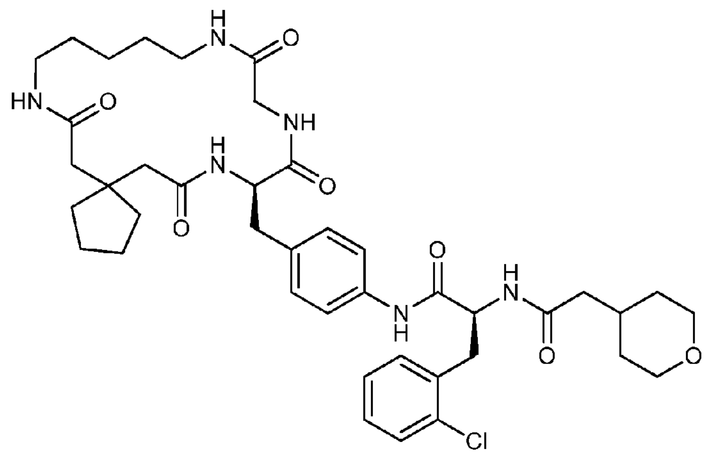
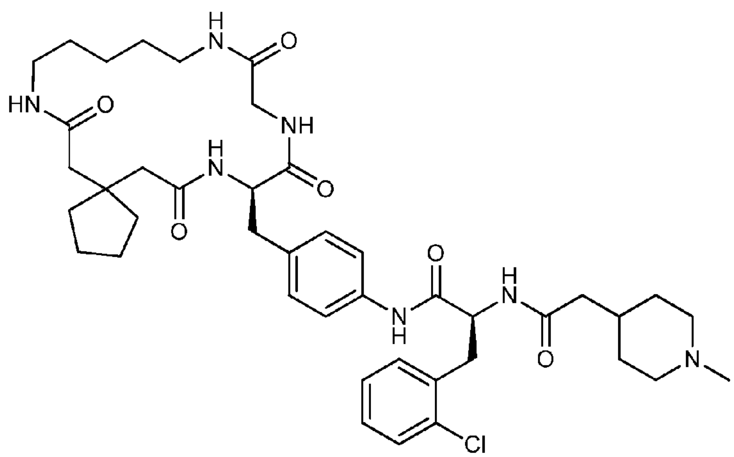
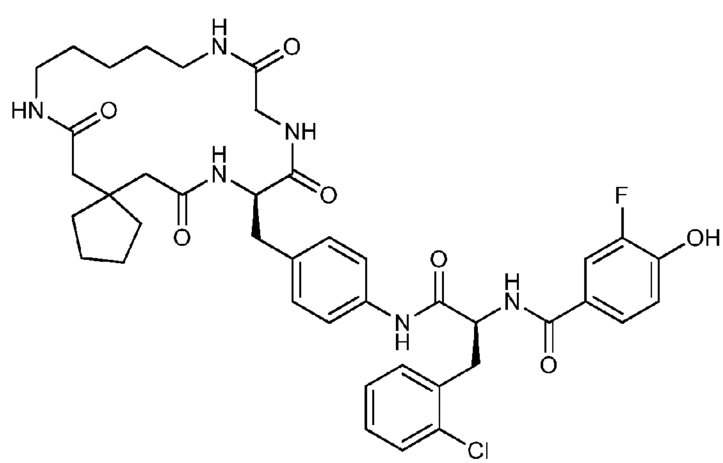
Compound No.	Structure
275	
276	
277	

FIG. 12-80

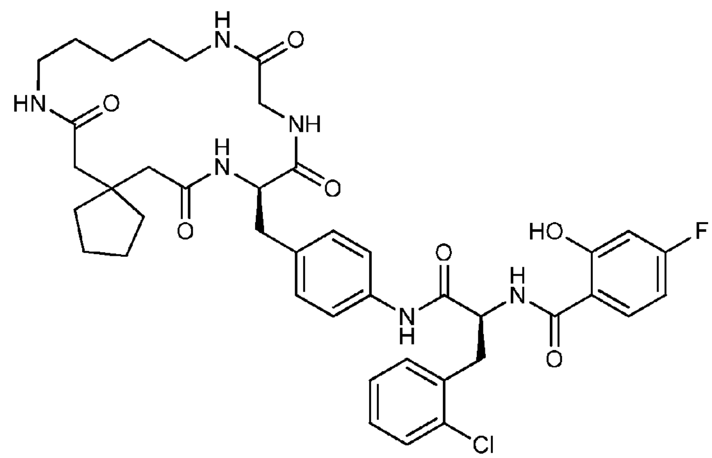
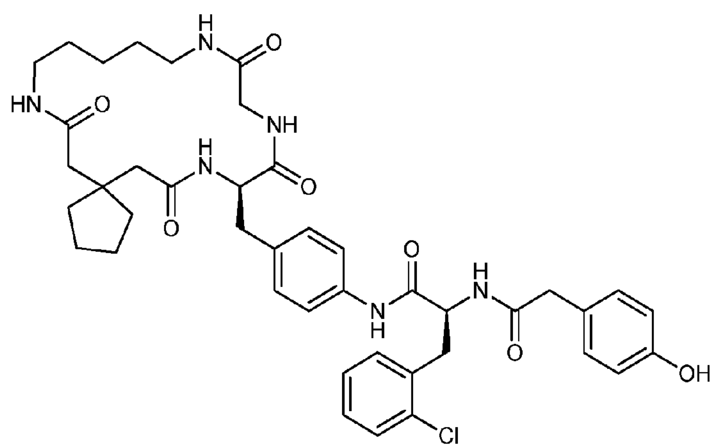
Compound No.	Structure
278	
279	

FIG. 12-81

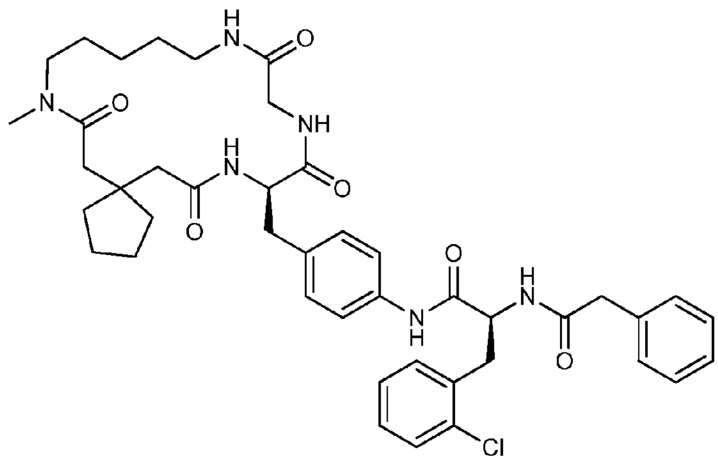
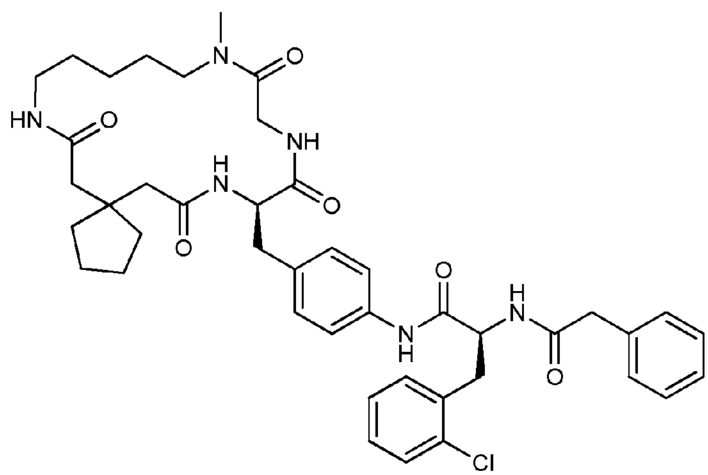
Compound No.	Structure
280	
281	

FIG. 12-82

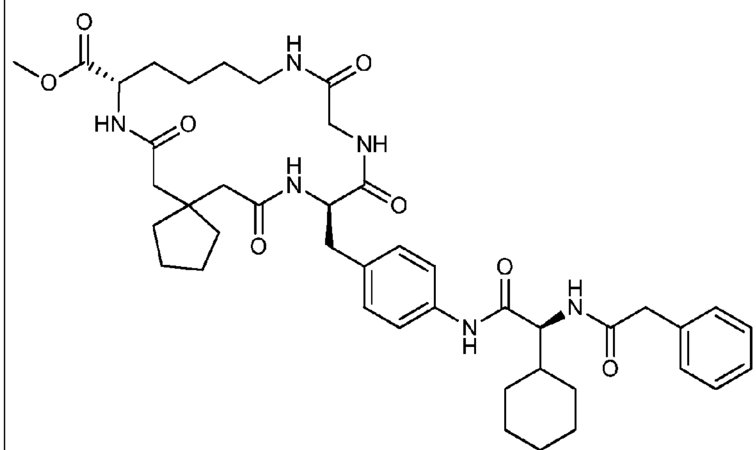
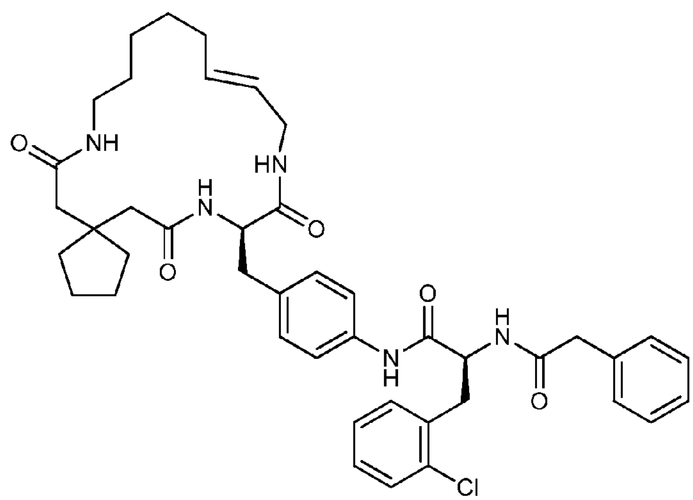
Compound No.	Structure
282	
283	

FIG. 12-83

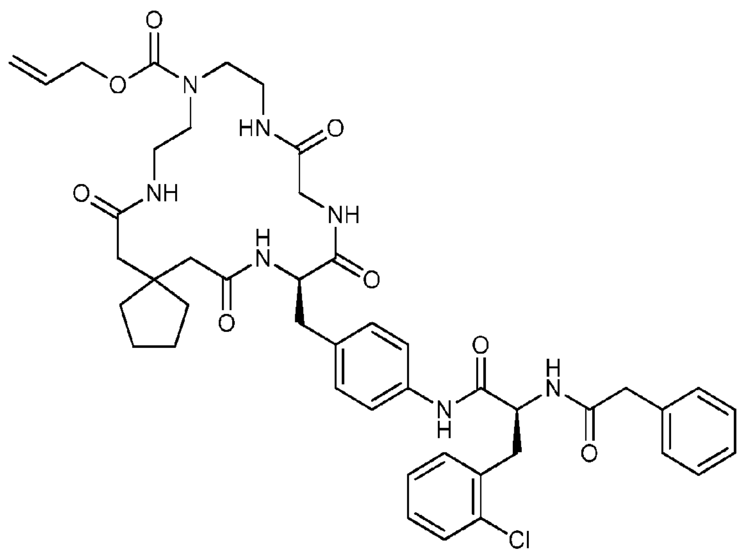
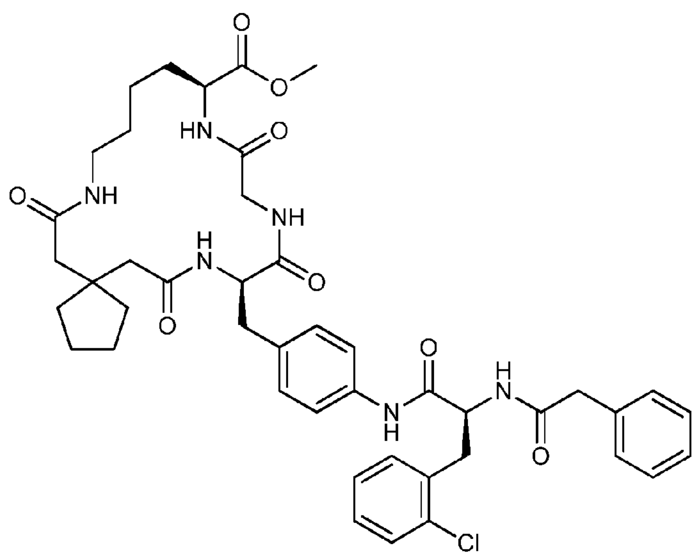
Compound No.	Structure
284	
285	

FIG. 12-84

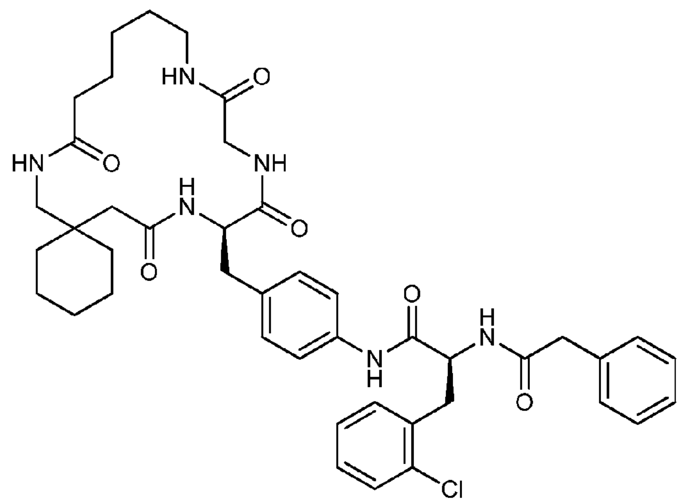
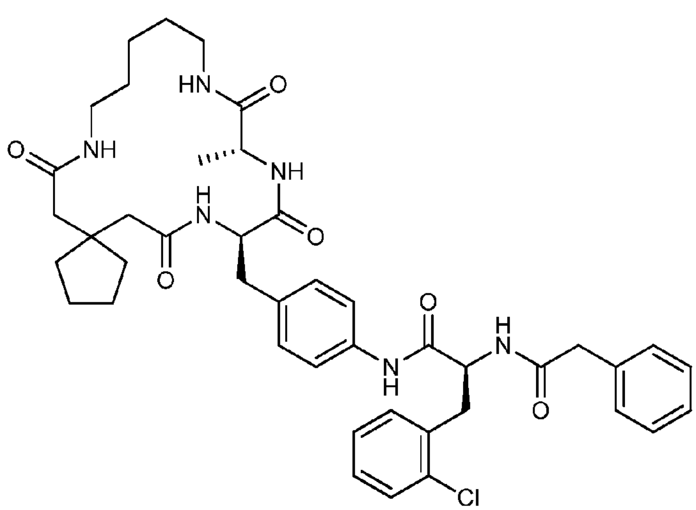
Compound No.	Structure
286	
288	

FIG. 12-85

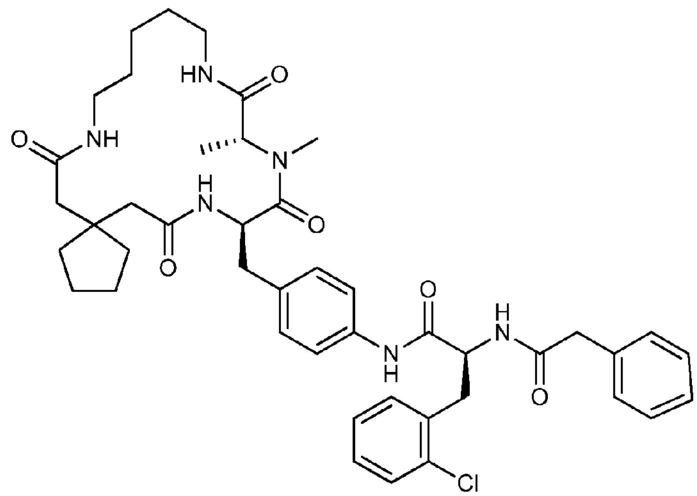
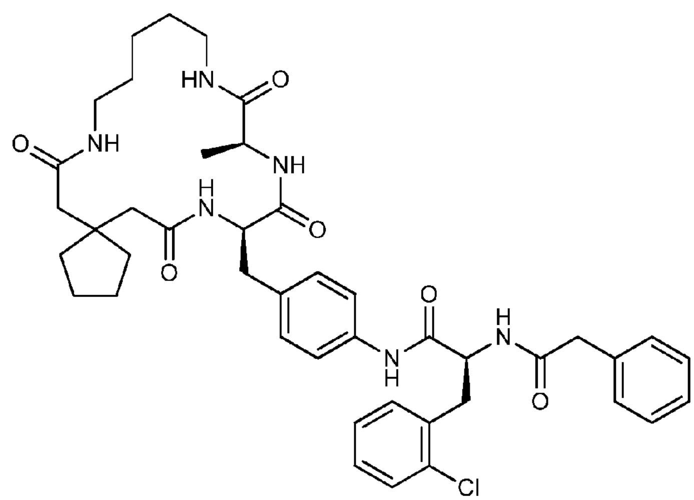
Compound No.	Structure
289	
290	

FIG. 12-86

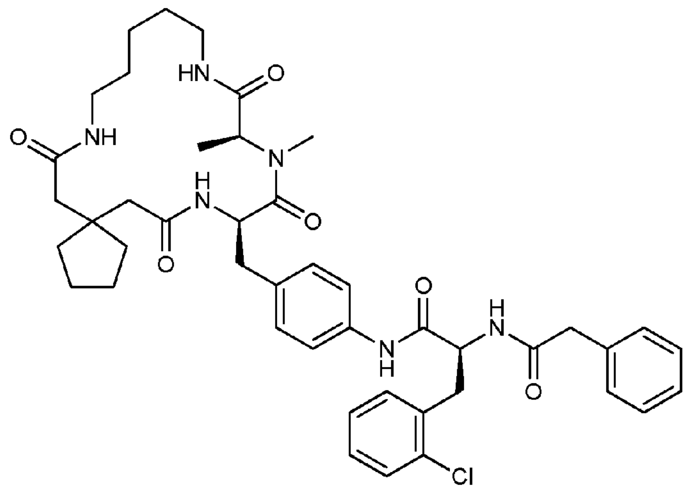
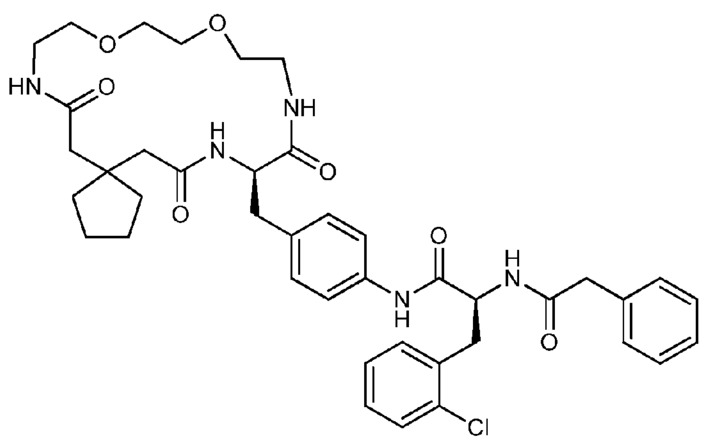
Compound No.	Structure
291	
292	

FIG. 12-87

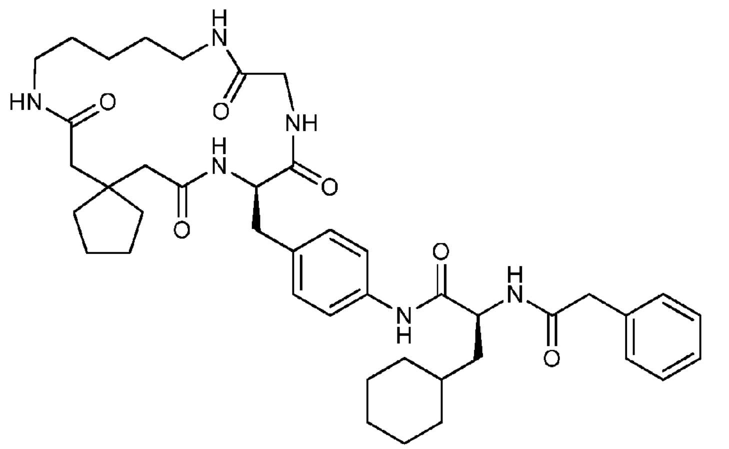
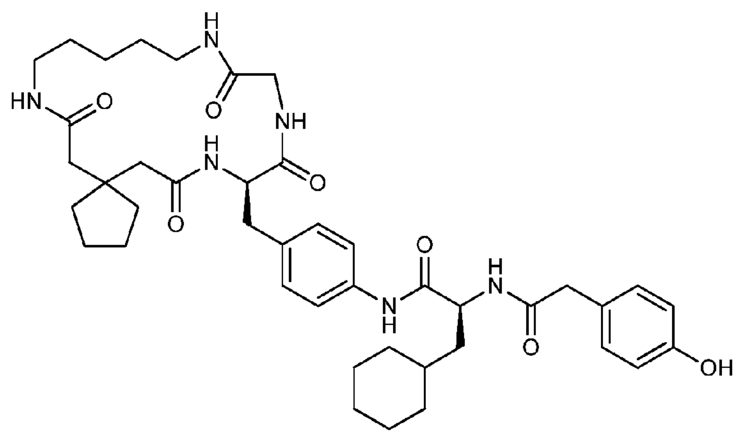
Compound No.	Structure
293	
294	

FIG. 12-88

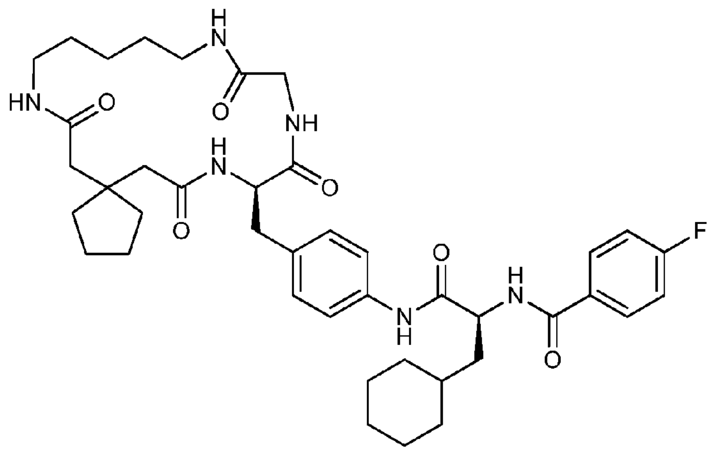
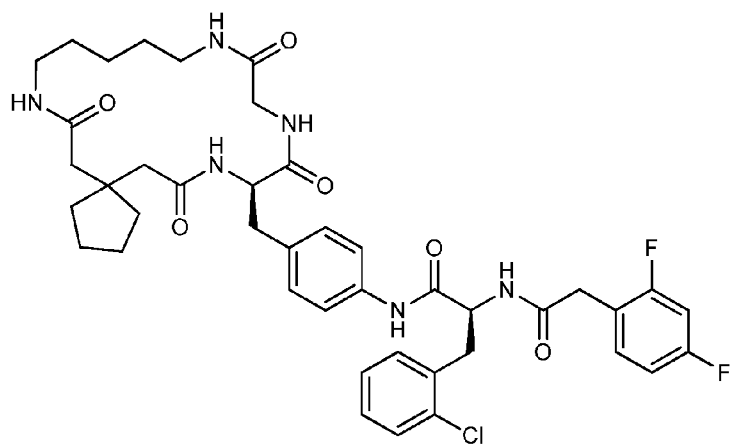
Compound No.	Structure
295	
296	

FIG. 12-89

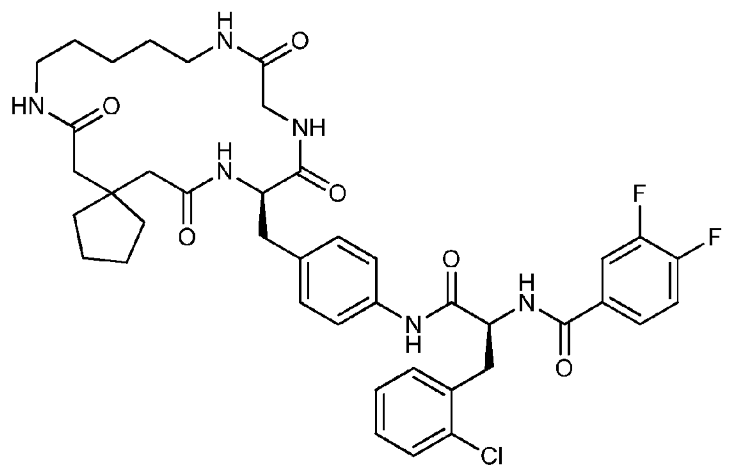
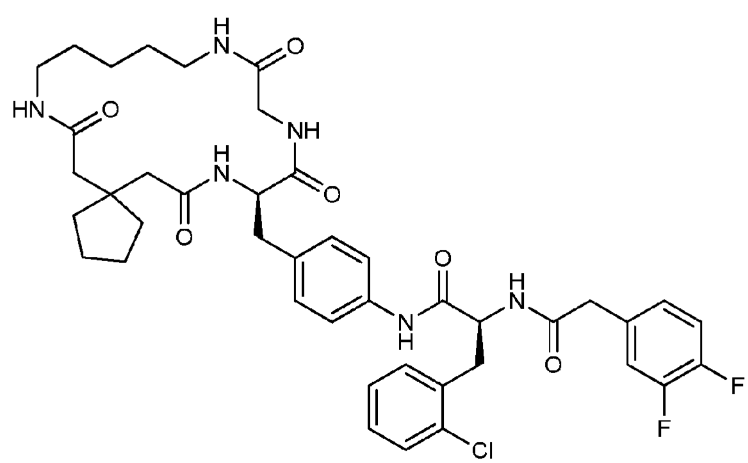
Compound No.	Structure
297	
298	

FIG. 12-90

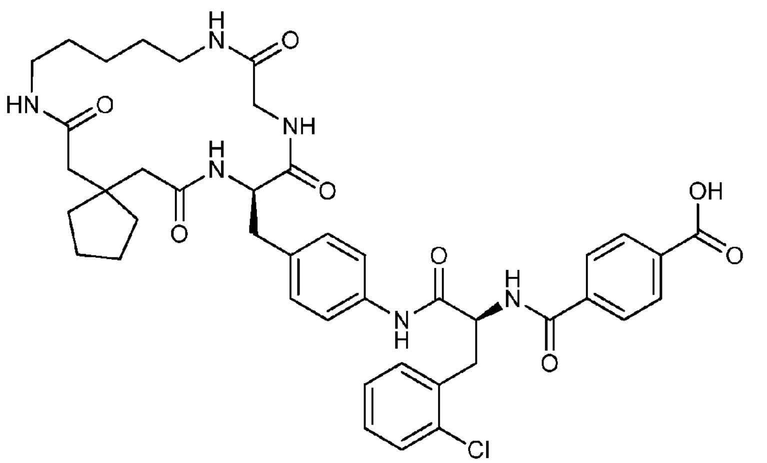
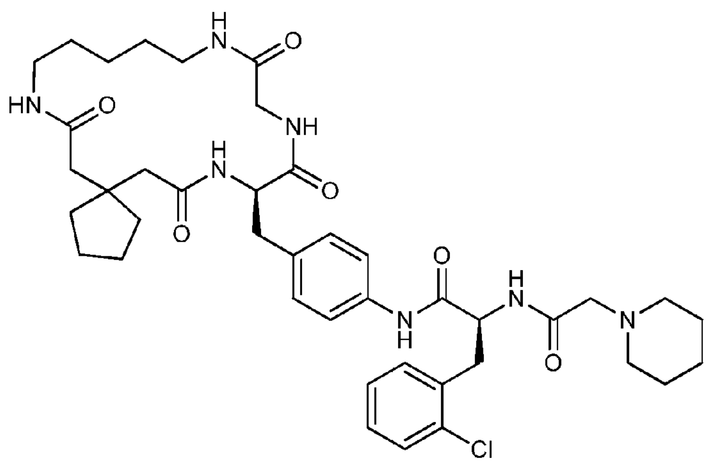
Compound No.	Structure
299	
300	

FIG. 12-91

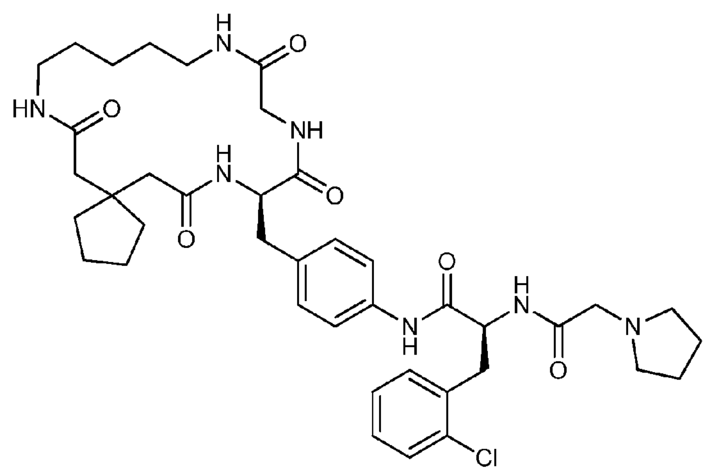
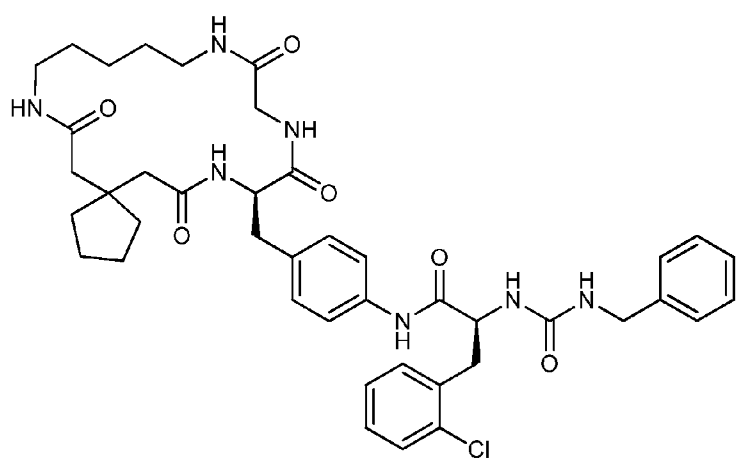
Compound No.	Structure
301	
302	

FIG. 12-92

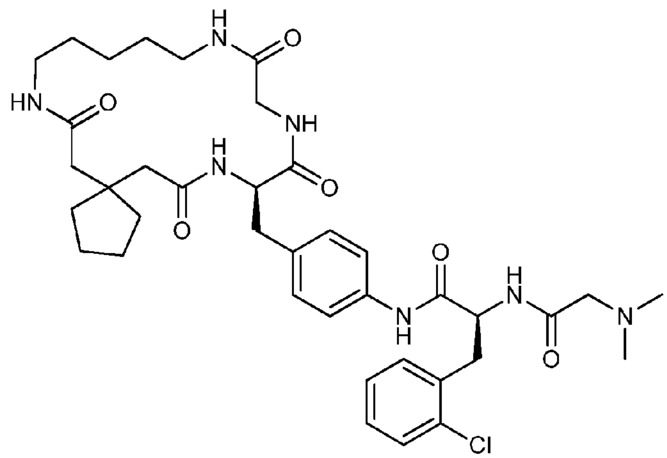
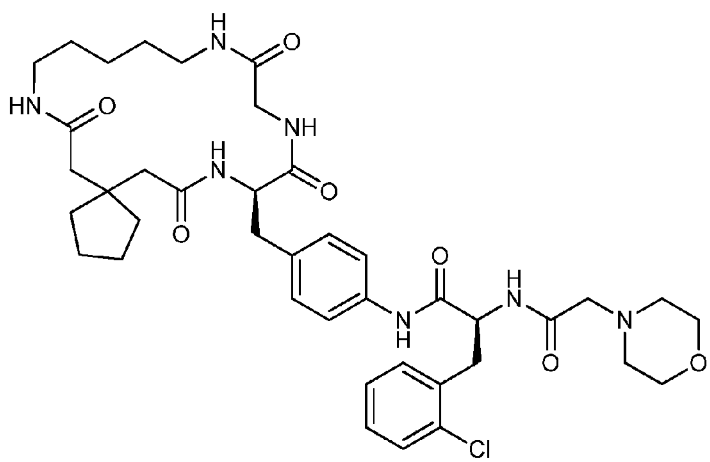
Compound No.	Structure
303	
304	

FIG. 12-93

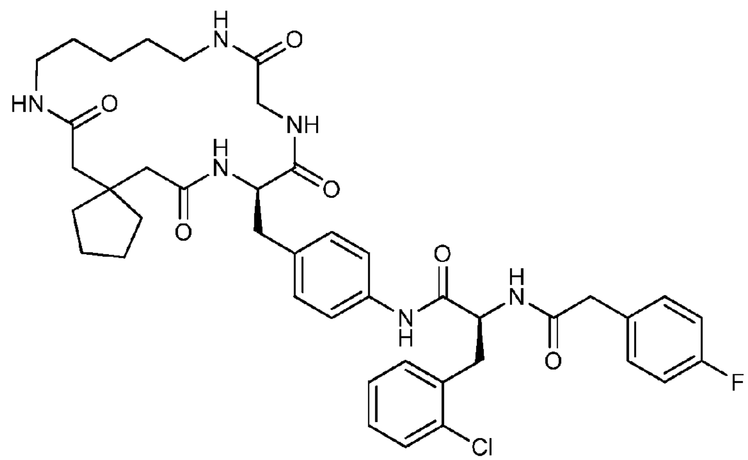
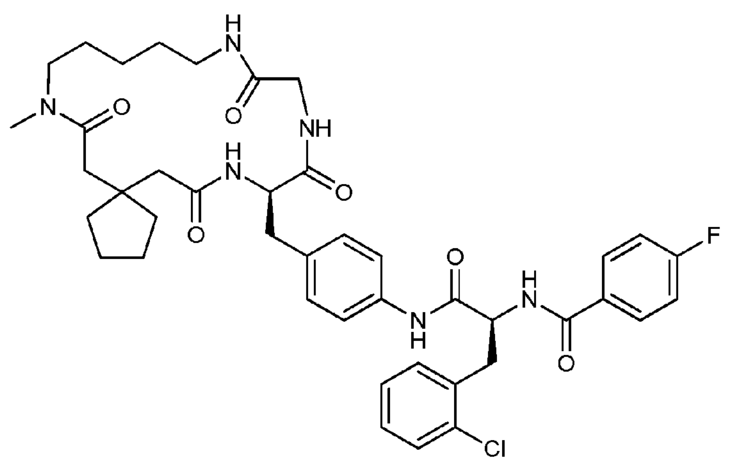
Compound No.	Structure
305	
306	

FIG. 12-94

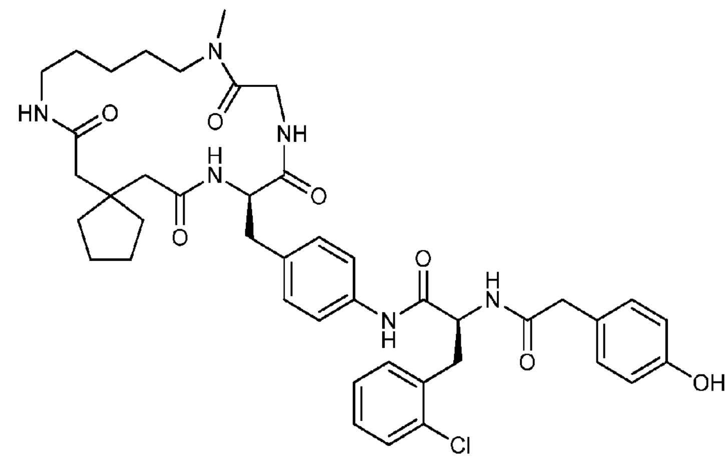
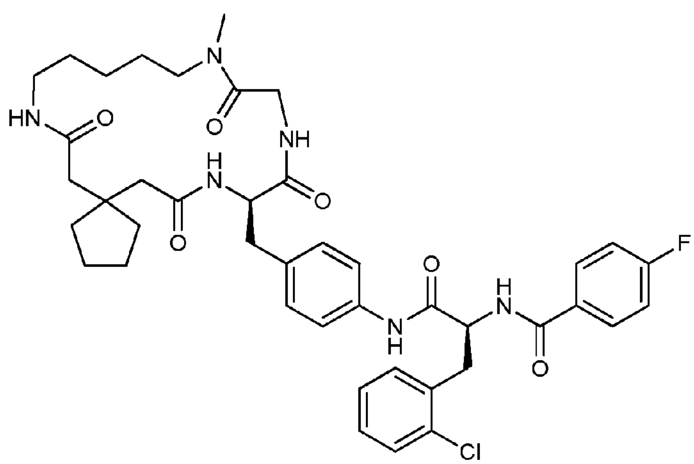
Compound No.	Structure
307	
308	

FIG. 12-95

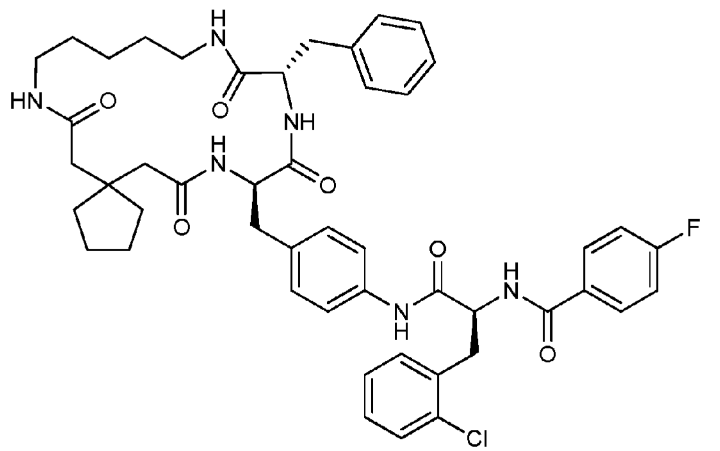
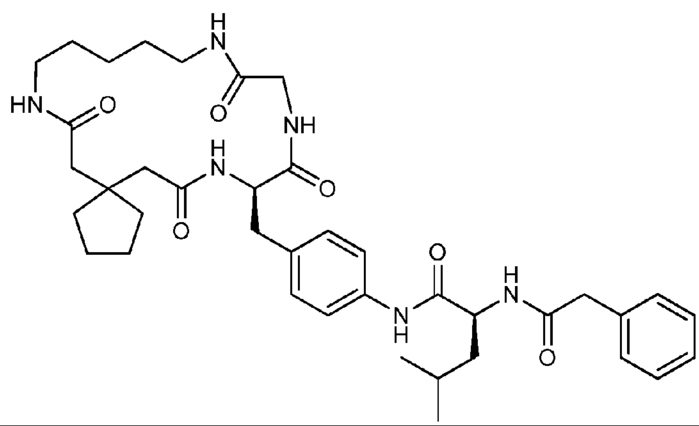
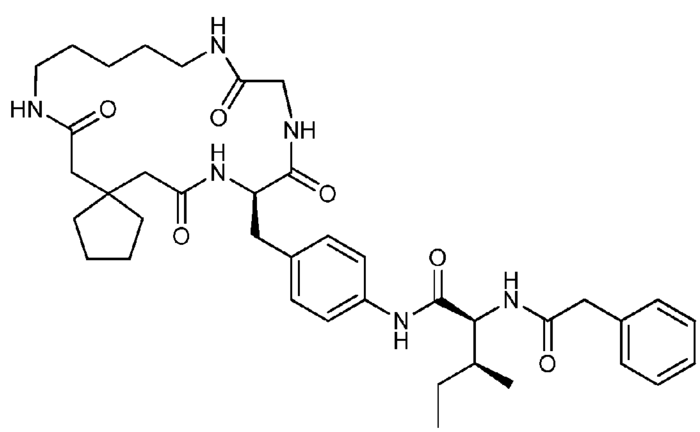
Compound No.	Structure
309	
310	
311	

FIG. 12-96

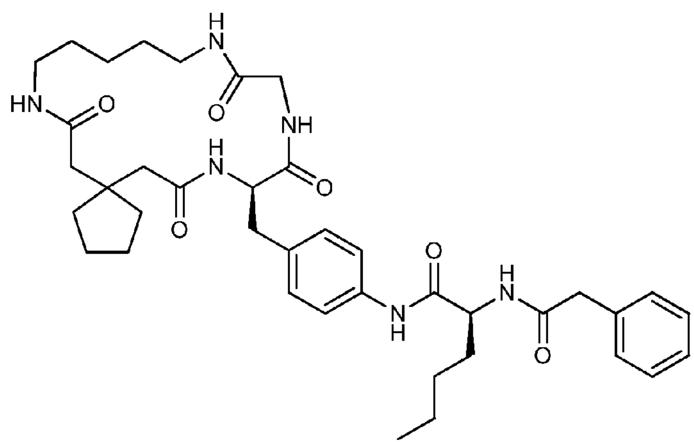
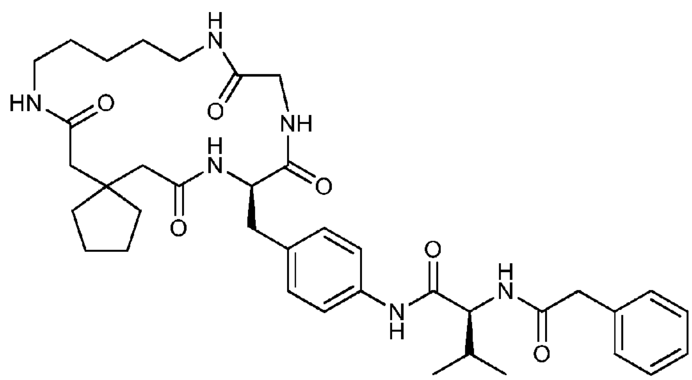
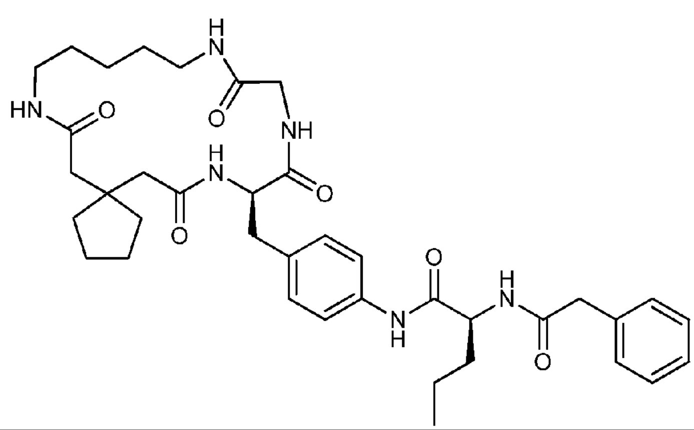
Compound No.	Structure
312	
313	
314	

FIG. 12-97

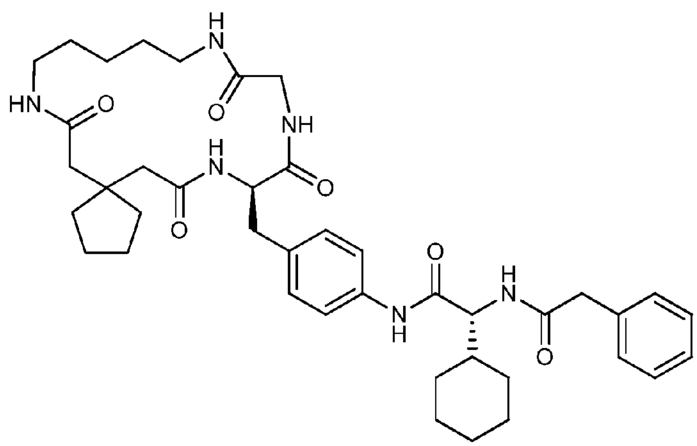
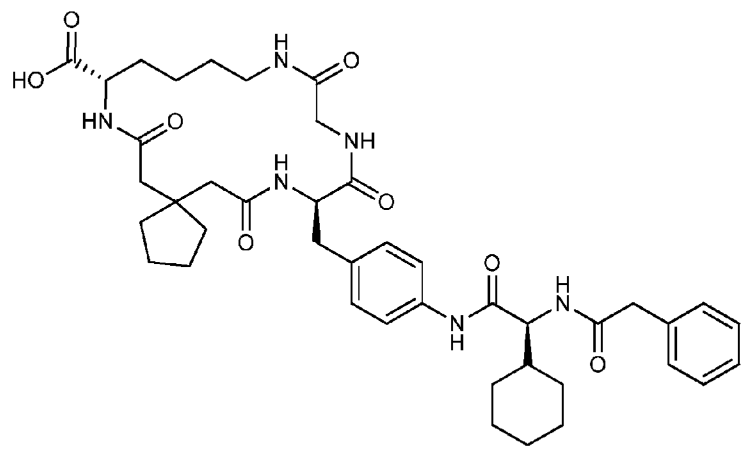
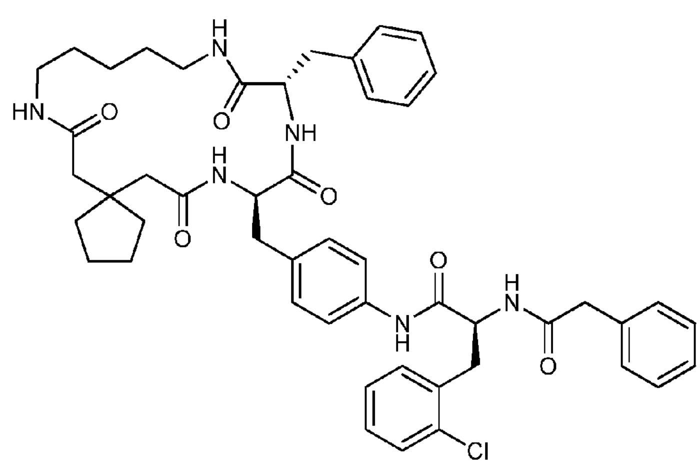
Compound No.	Structure
315	
316	
317	

FIG. 12-98

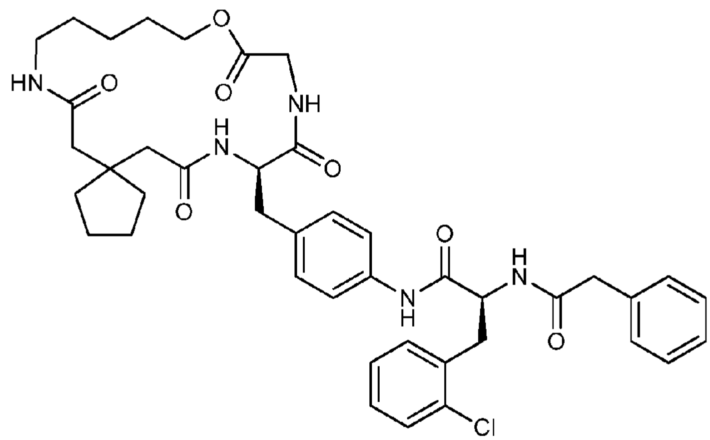
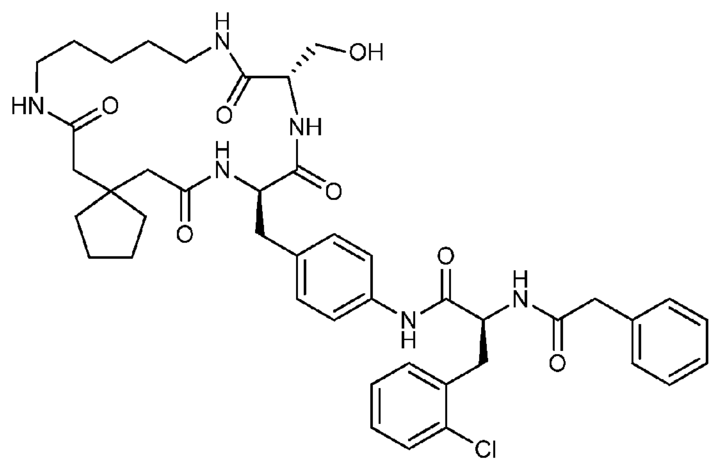
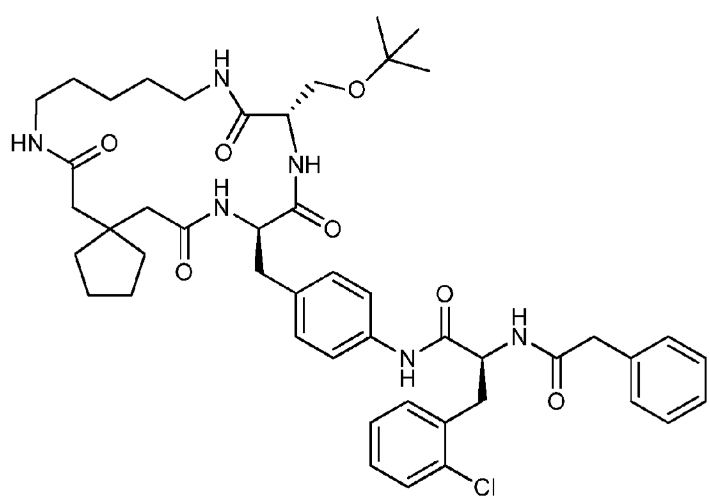
Compound No.	Structure
318	
319	
320	

FIG. 12-99

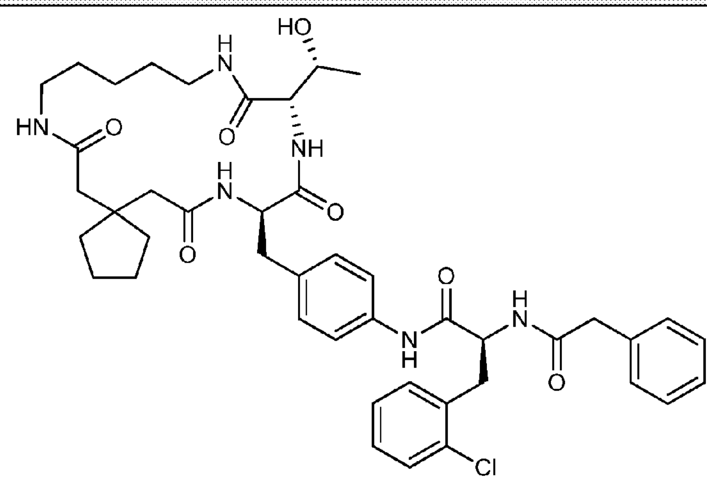
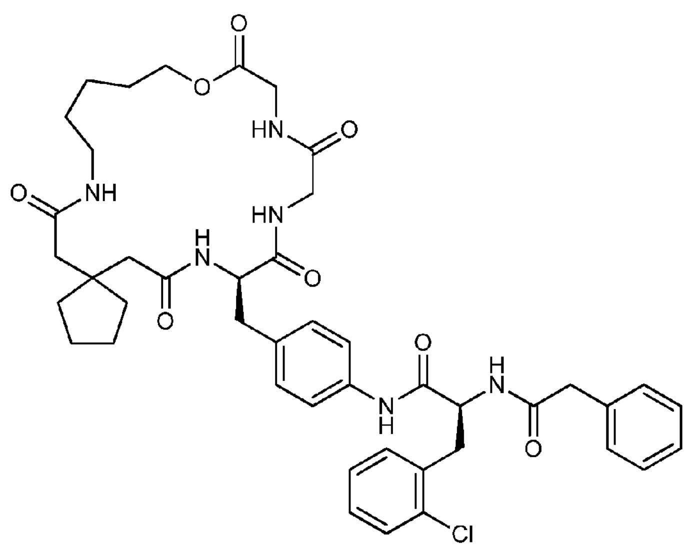
Compound No.	Structure
321	
322	

FIG. 12-100

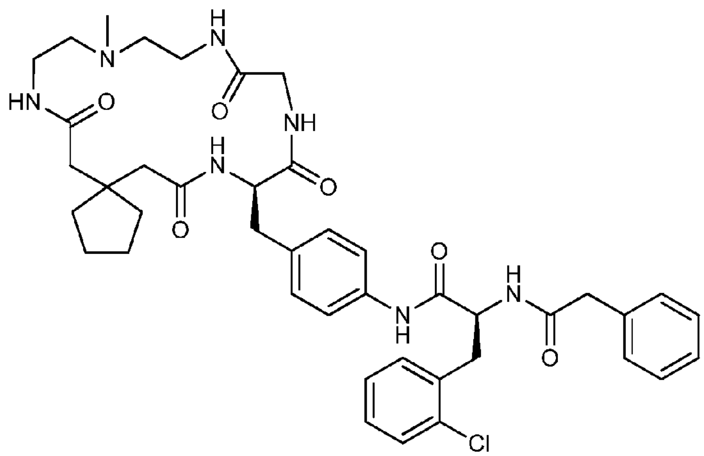
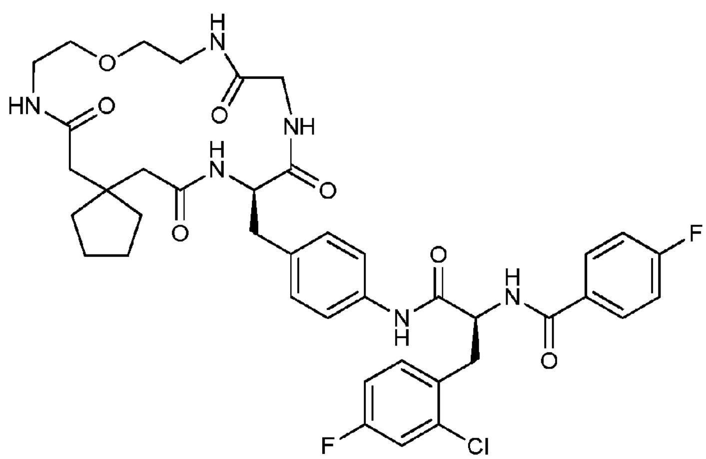
Compound No.	Structure
323	
324	

FIG. 12-101

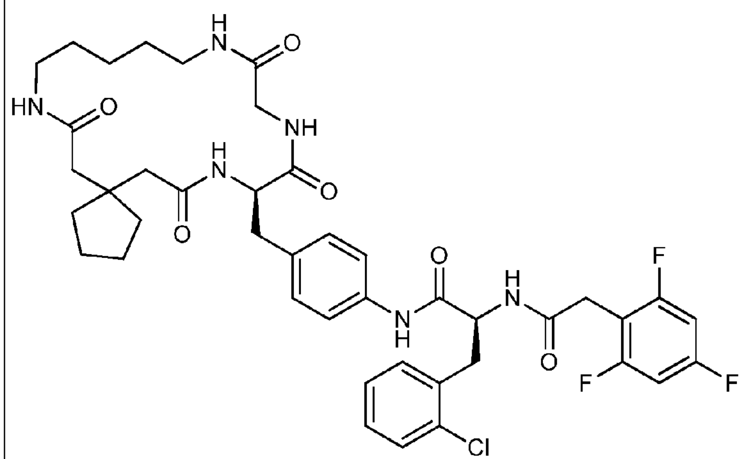
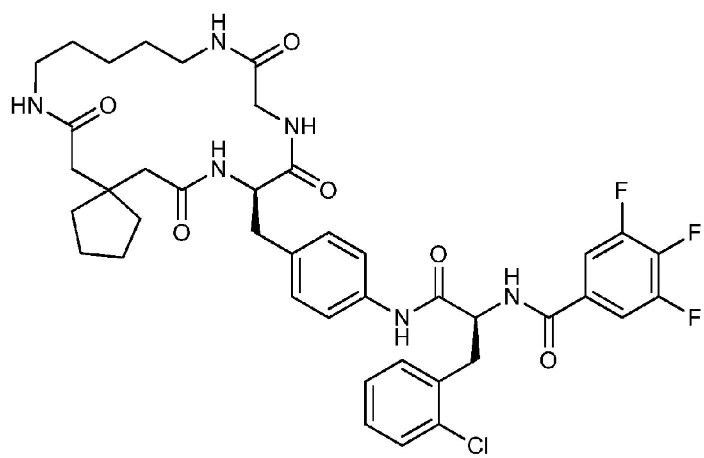
Compound No.	Structure
325	
326	

FIG. 12-102

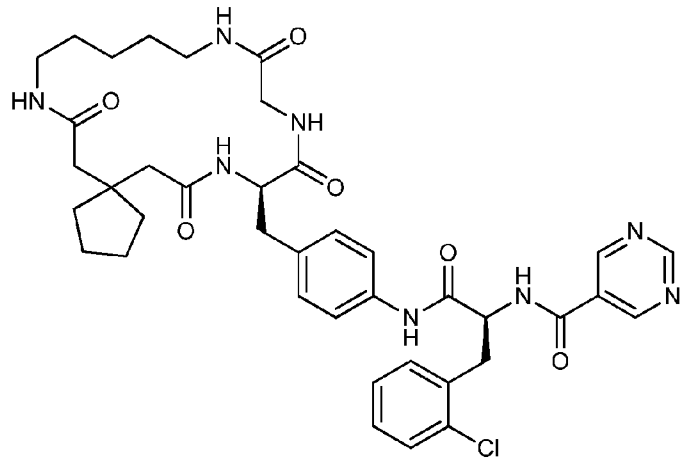
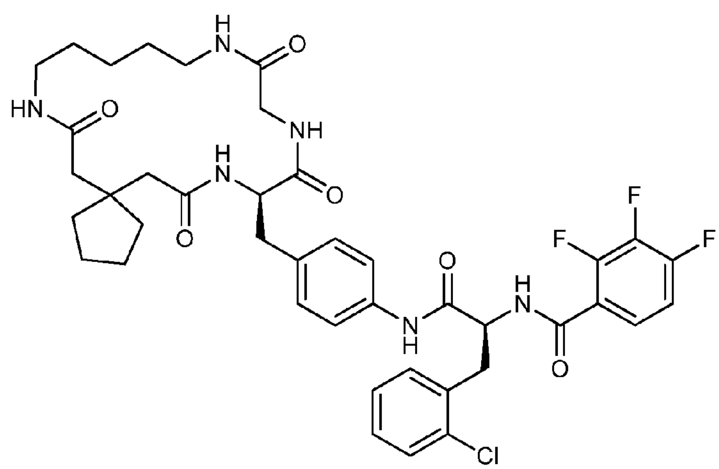
Compound No.	Structure
327	
328	

FIG. 12-103

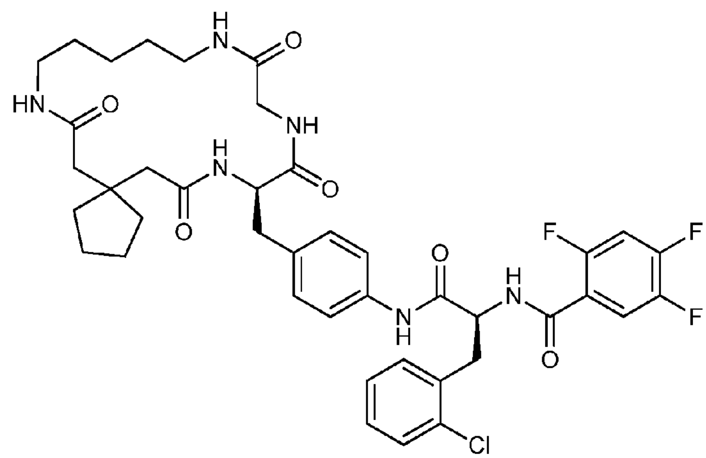
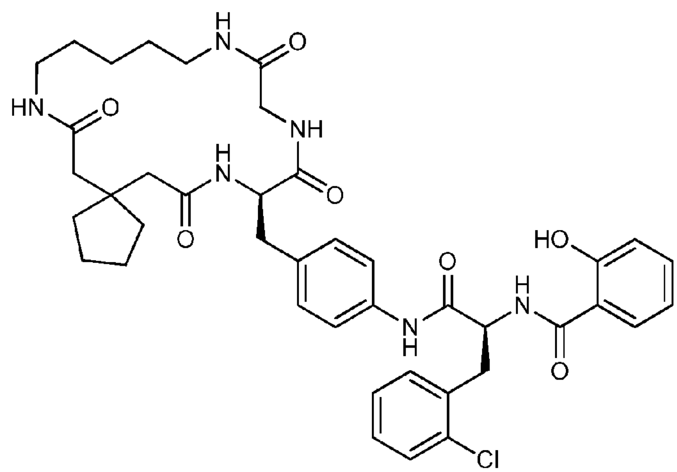
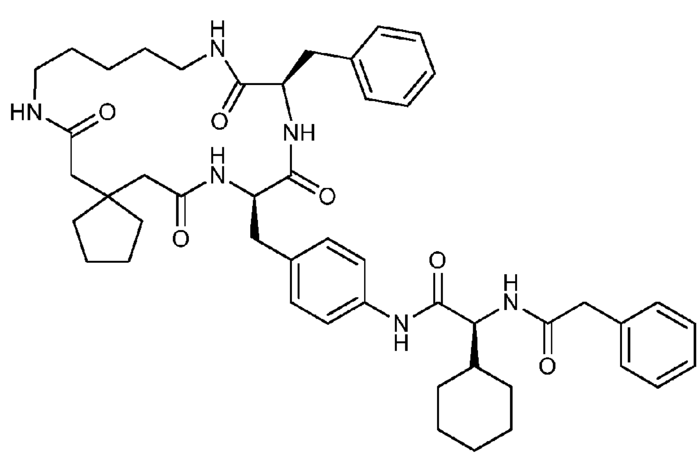
Compound No.	Structure
329	
330	
331	

FIG. 12-104

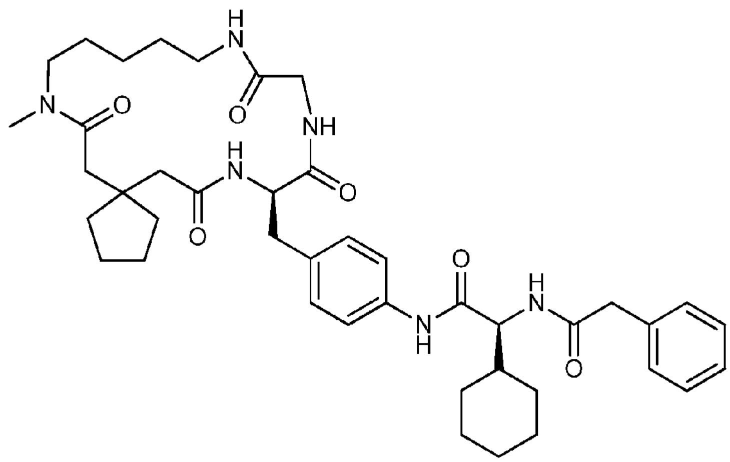
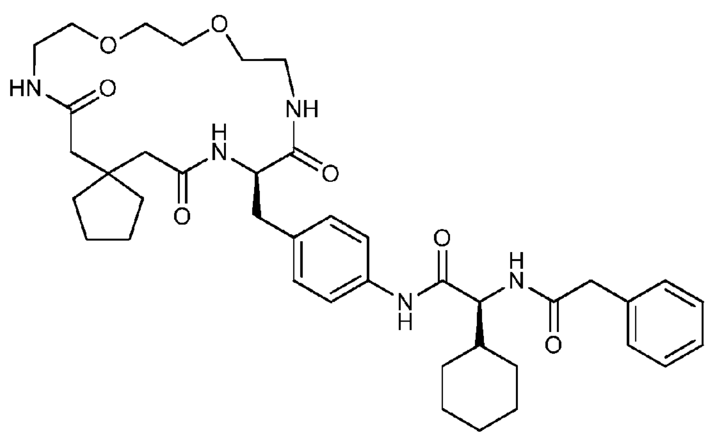
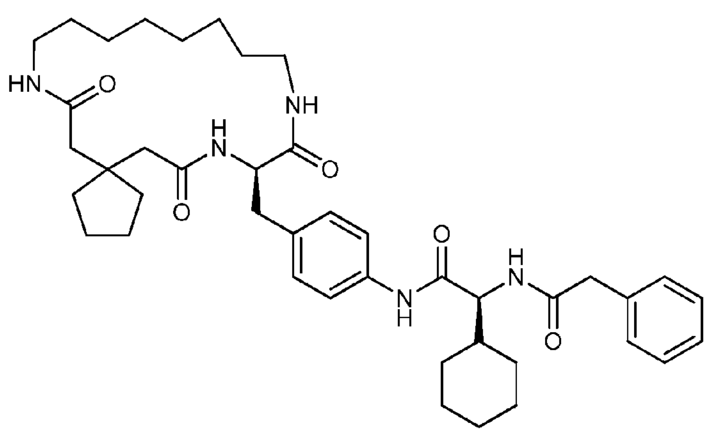
Compound No.	Structure
332	
333	
334	

FIG. 12-105

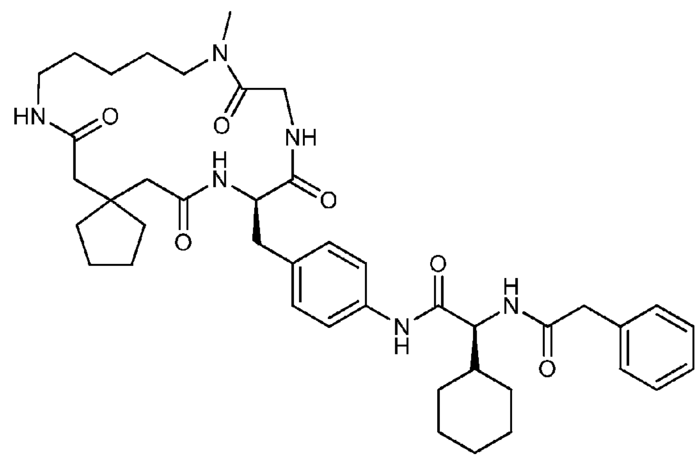
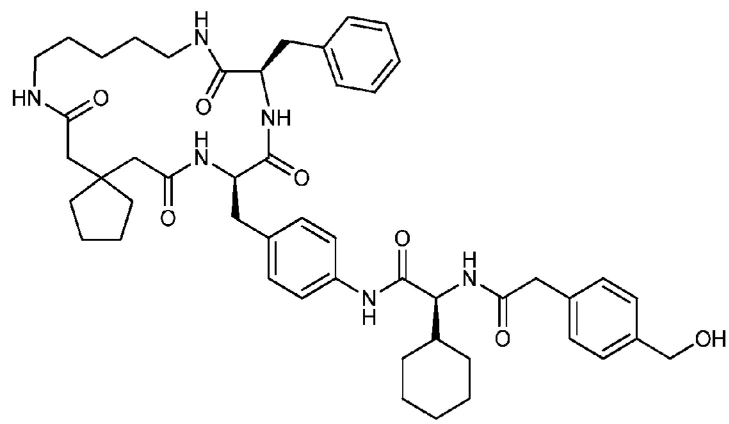
Compound No.	Structure
335	
336	

FIG. 12-106

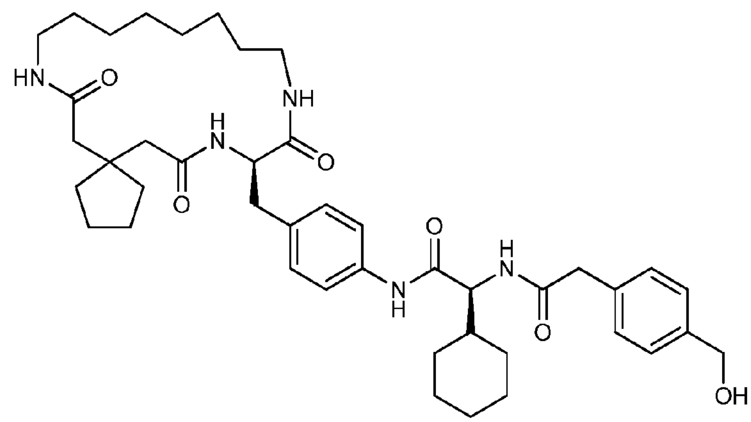
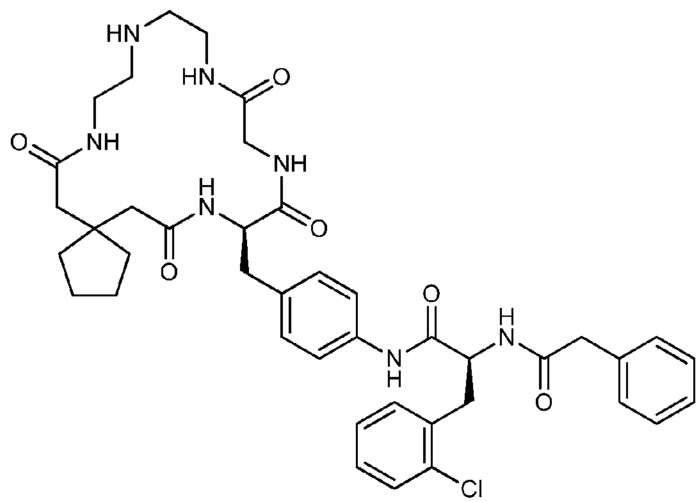
Compound No.	Structure
337	
338	

FIG. 12-107

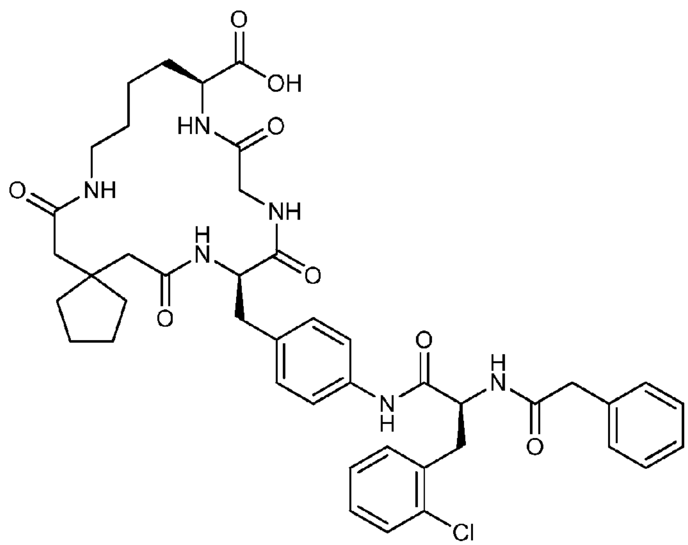
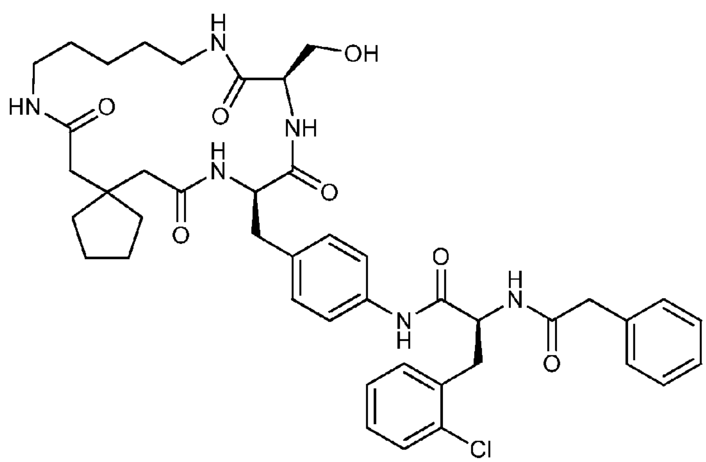
Compound No.	Structure
339	
340	

FIG. 12-108

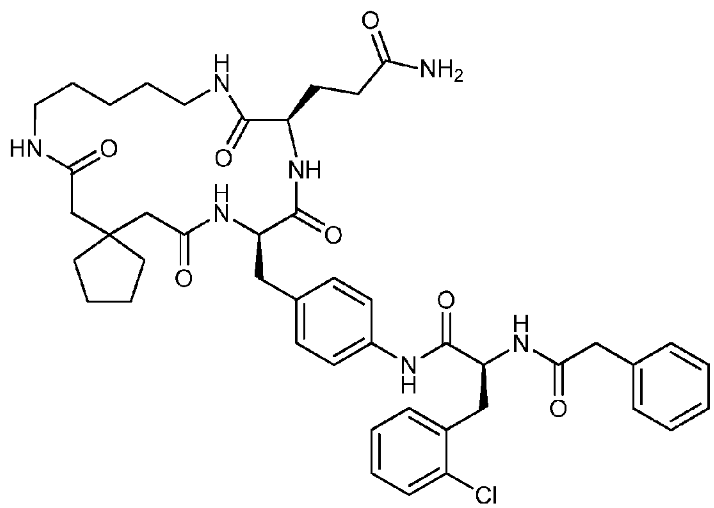
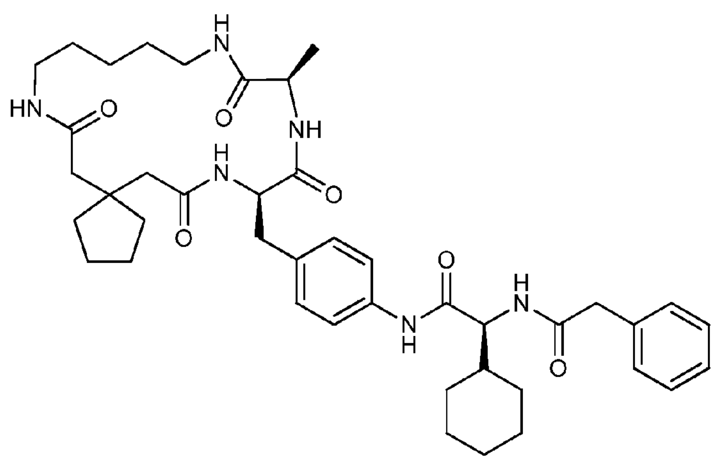
Compound No.	Structure
341	
342	

FIG. 12-109

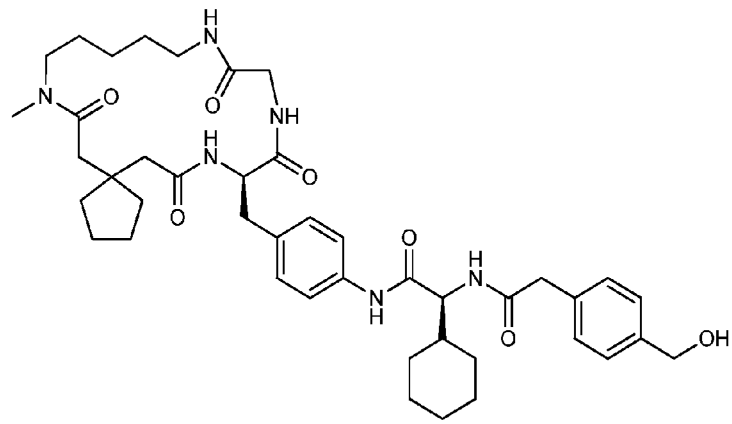
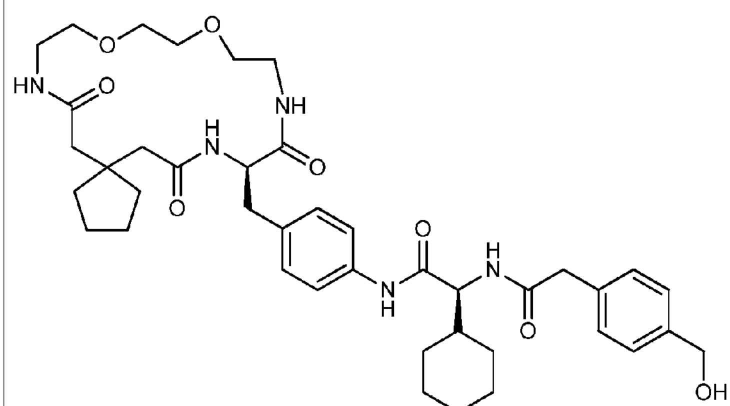
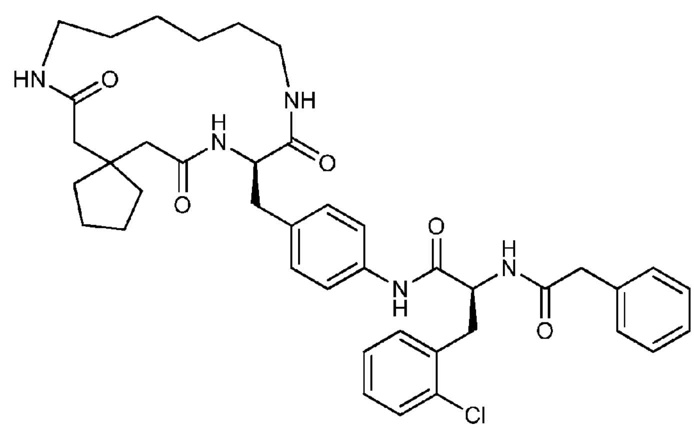
Compound No.	Structure
343	
344	
345	

FIG. 12-110

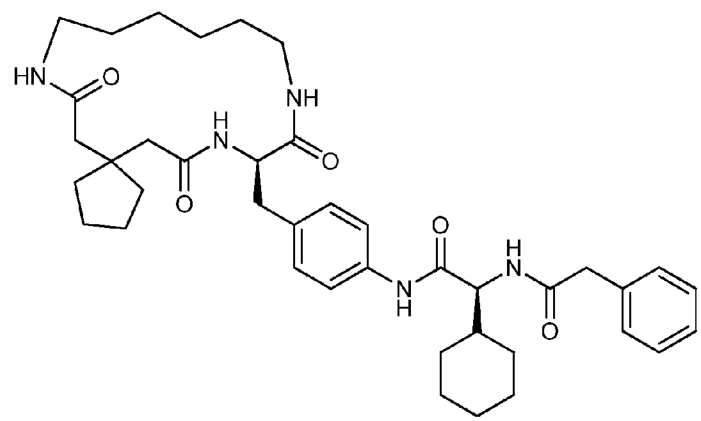
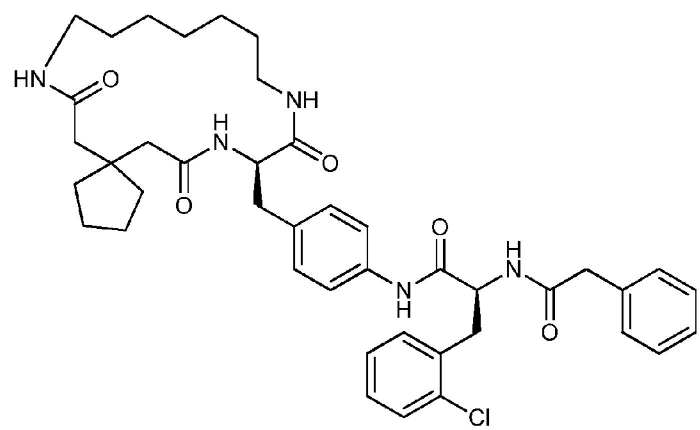
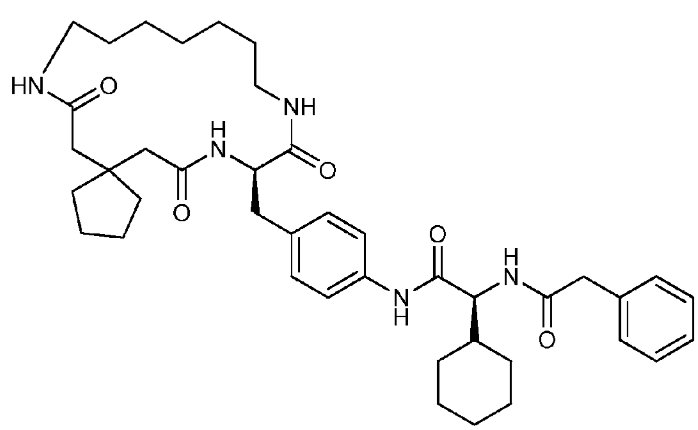
Compound No.	Structure
346	
347	
348	

FIG. 12-111

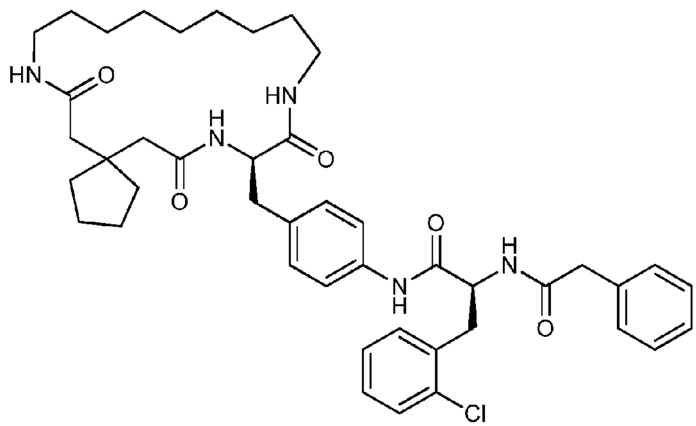
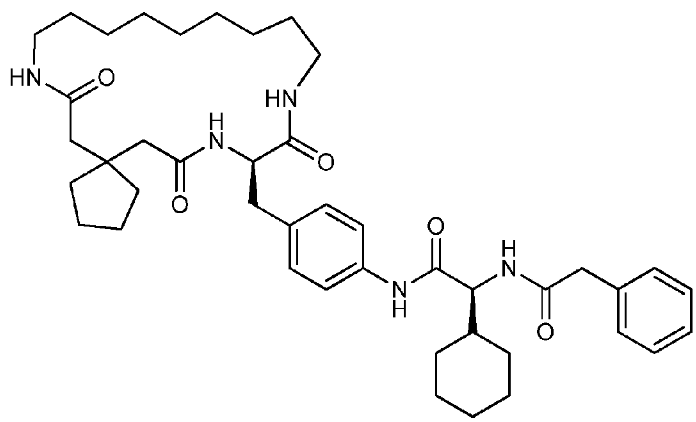
Compound No.	Structure
349	
350	

FIG. 12-112

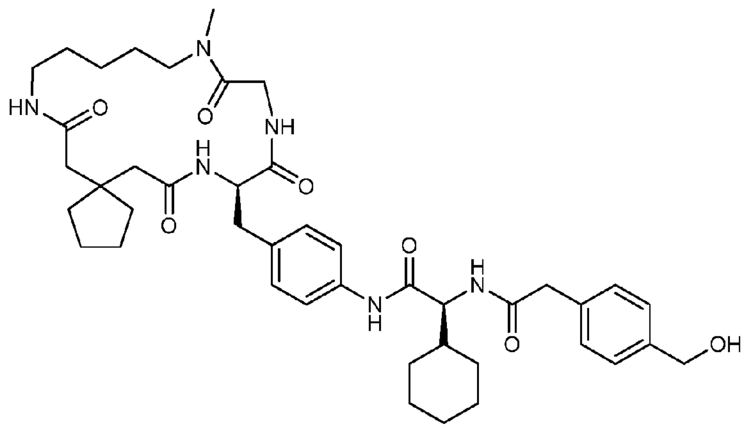
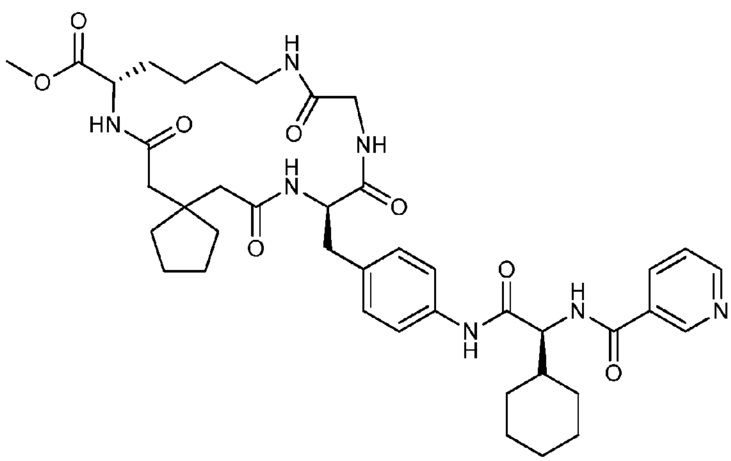
Compound No.	Structure
351	
352	

FIG. 12-113

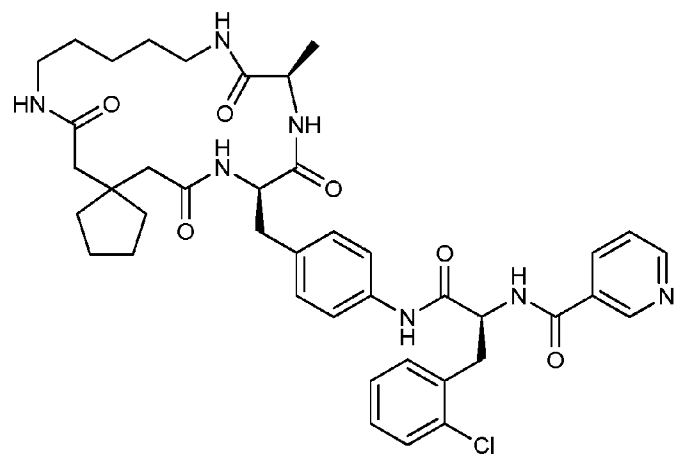
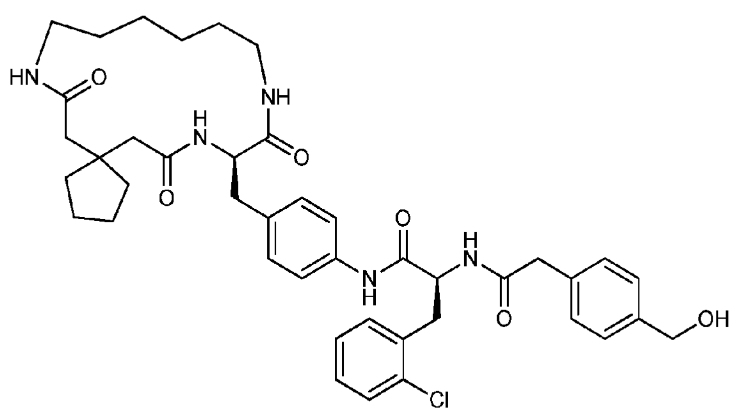
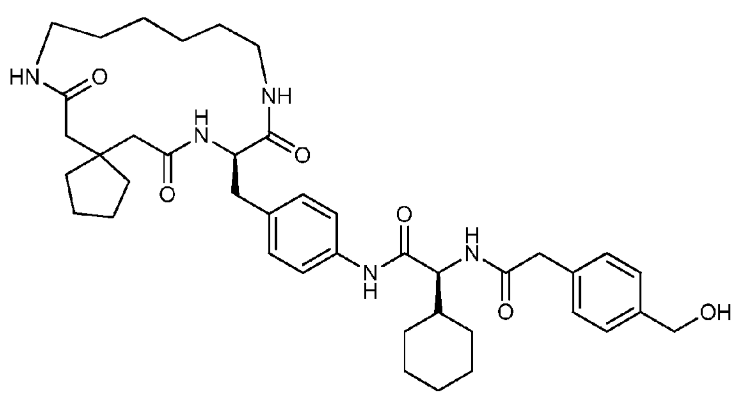
Compound No.	Structure
353	
354	
355	

FIG. 12-114

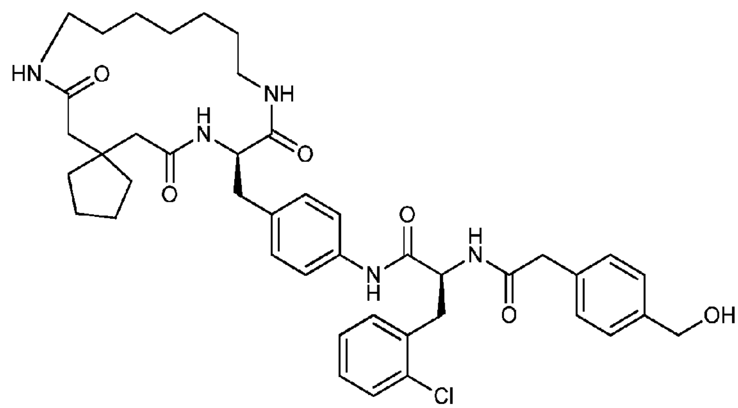
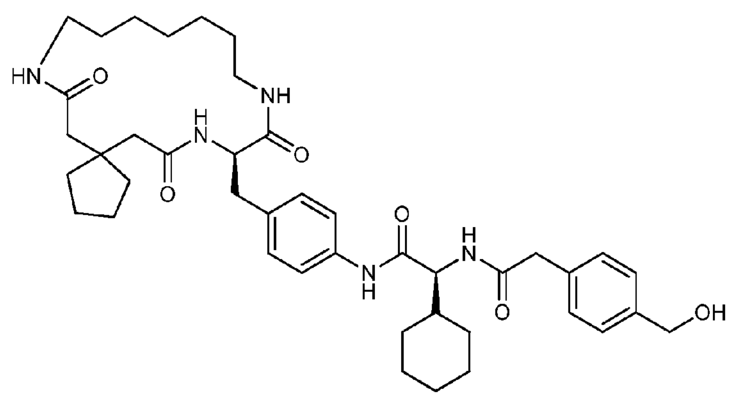
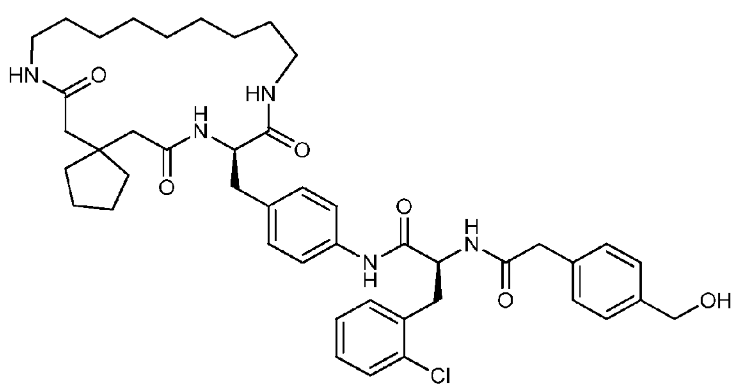
Compound No.	Structure
356	
357	
358	

FIG. 12-115

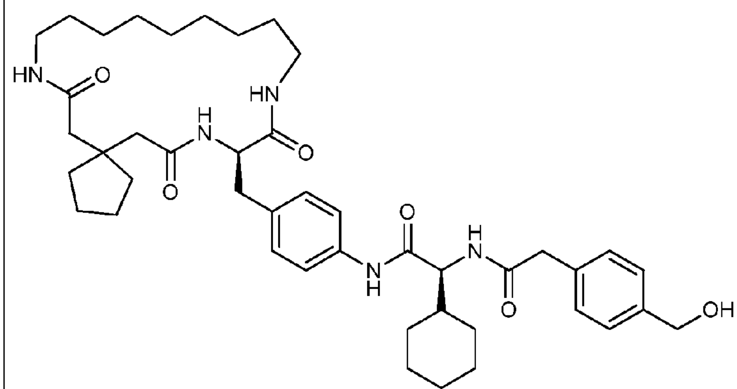
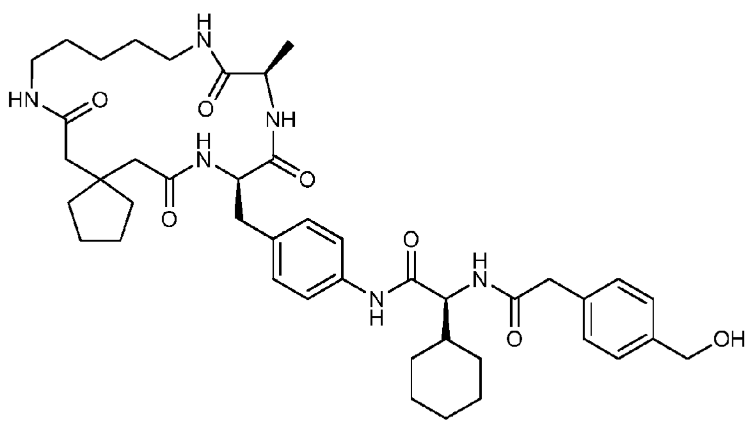
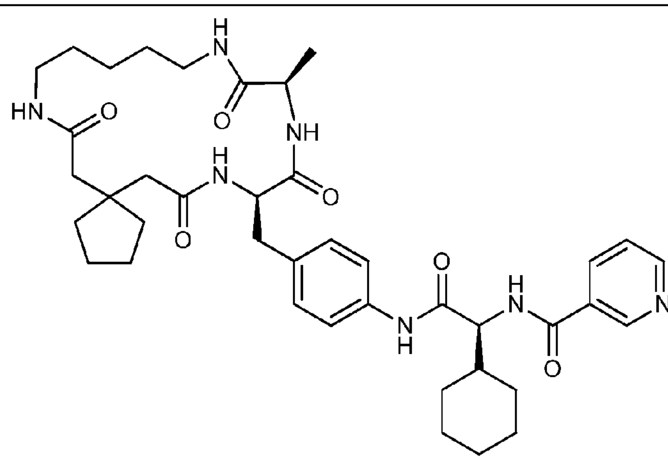
Compound No.	Structure
359	
360	
361	

FIG. 12-116

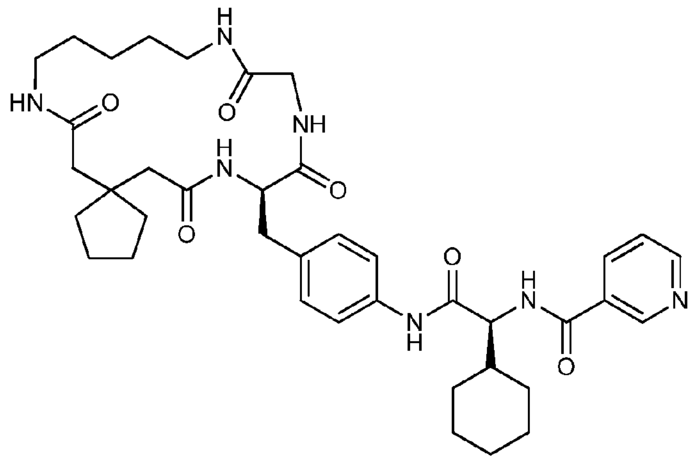
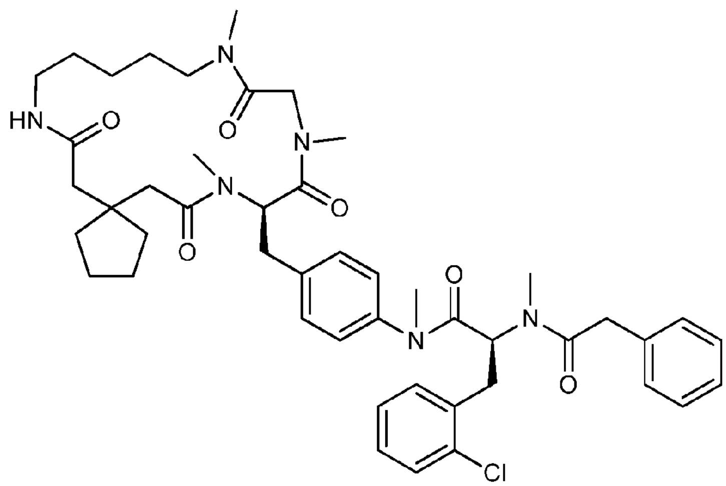
Compound No.	Structure
362	
363	

FIG. 12-117

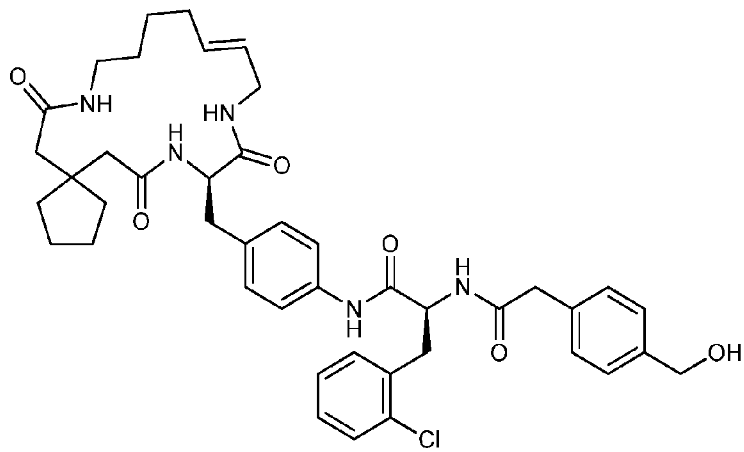
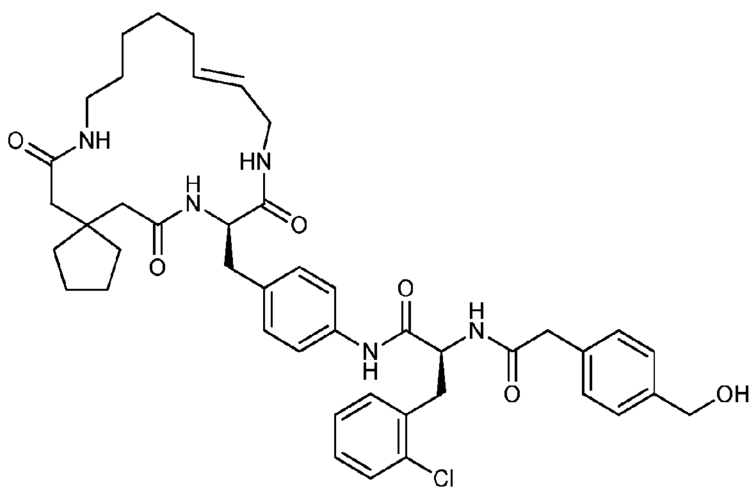
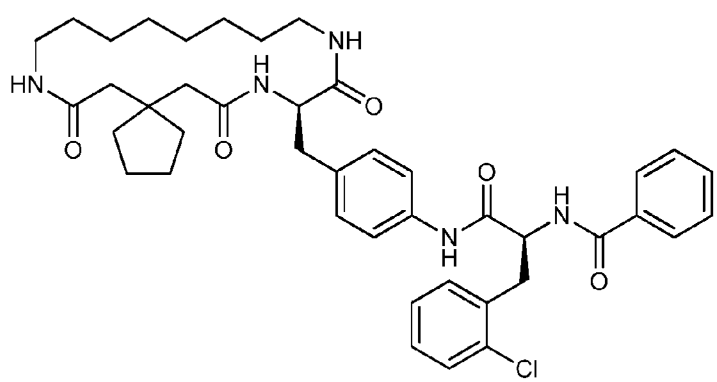
Compound No.	Structure
364	
365	
366	

FIG. 12-118

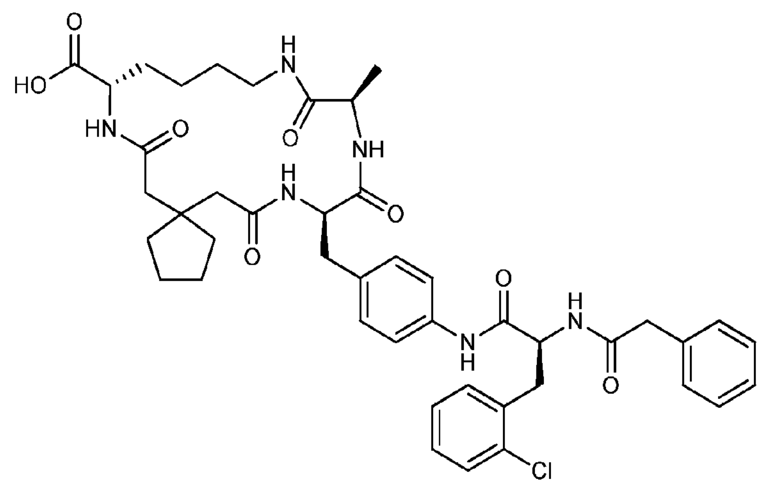
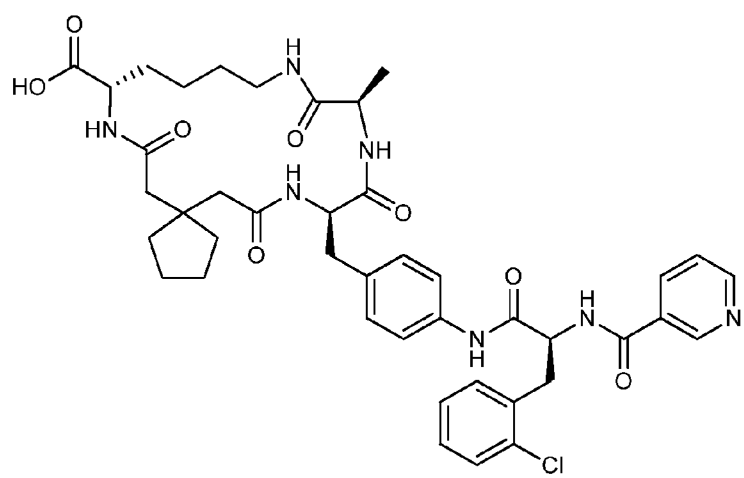
Compound No.	Structure
367	
368	

FIG. 12-119

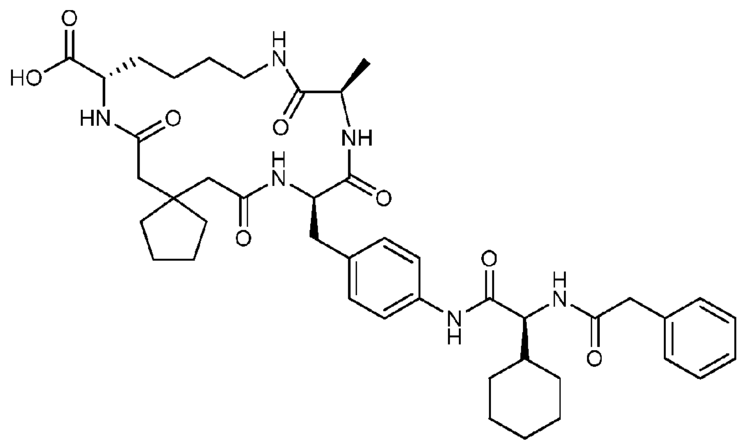
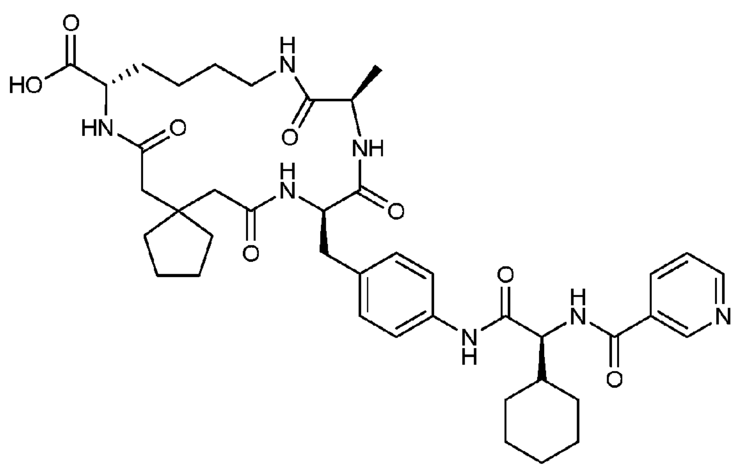
Compound No.	Structure
369	
370	

FIG. 12-120

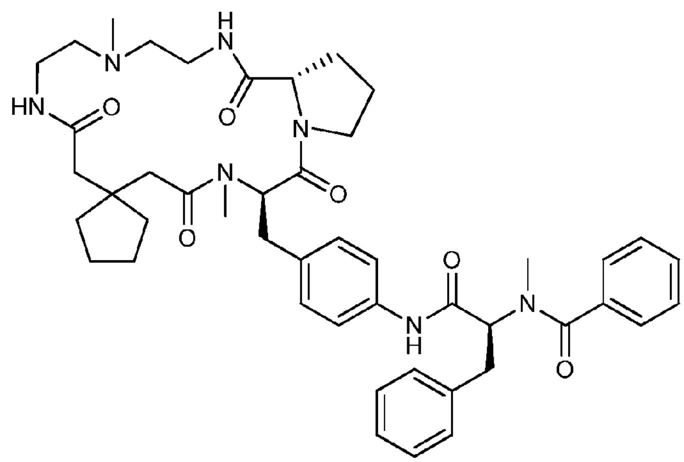
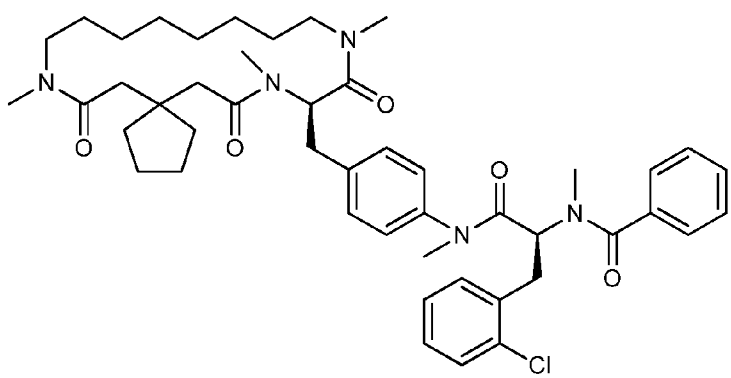
Compound No.	Structure
371	
372	

FIG. 12-121

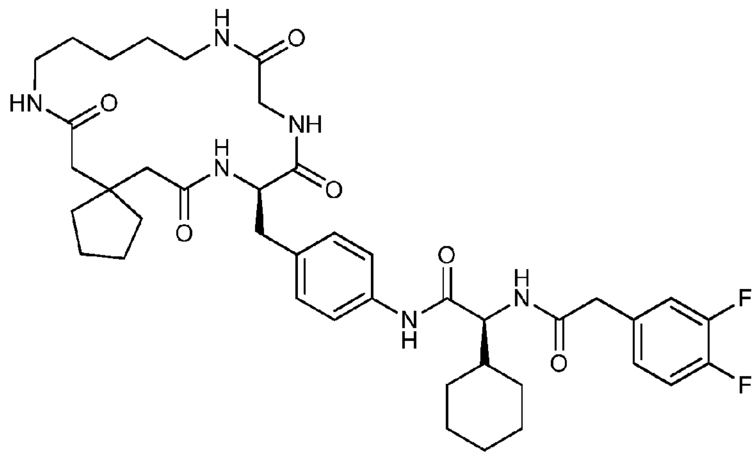
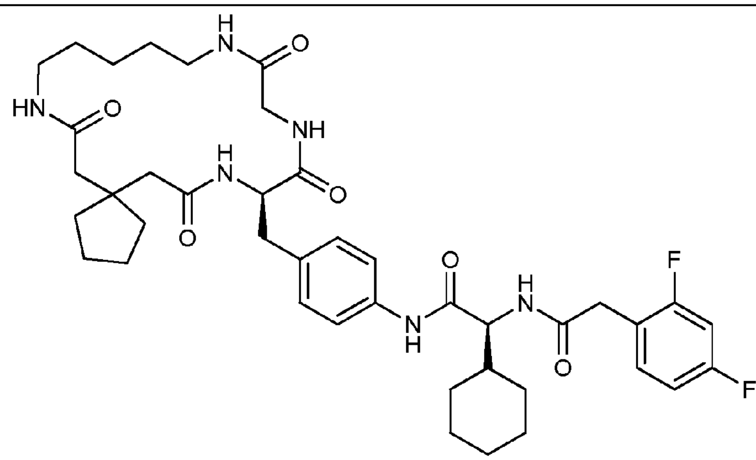
Compound No.	Structure
373	
374	

FIG. 12-122

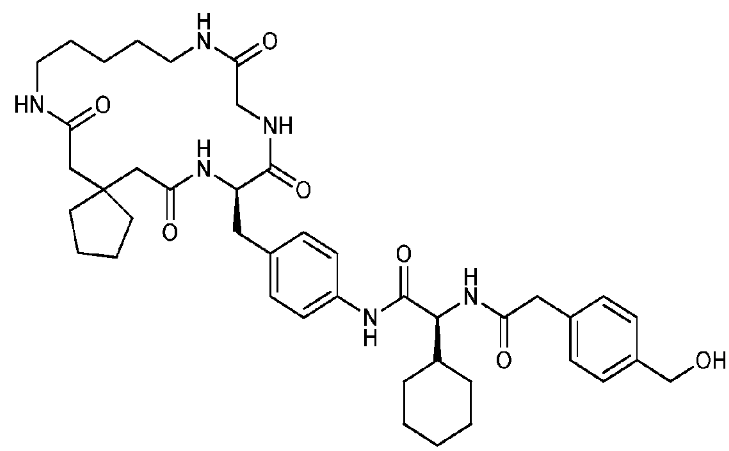
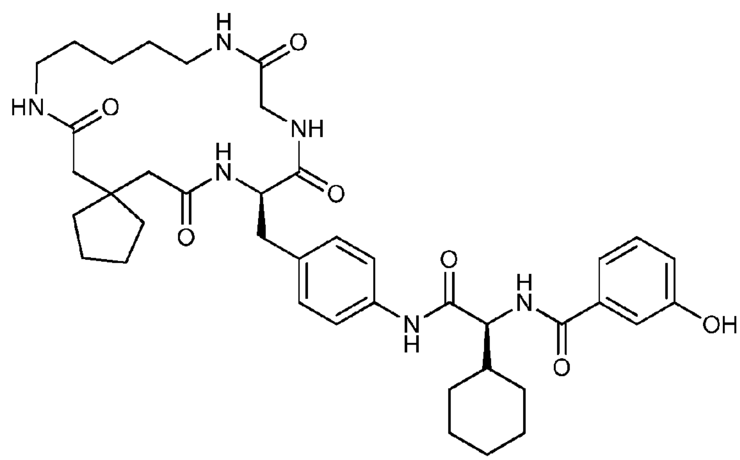
Compound No.	Structure
375	
376	

FIG. 12-123

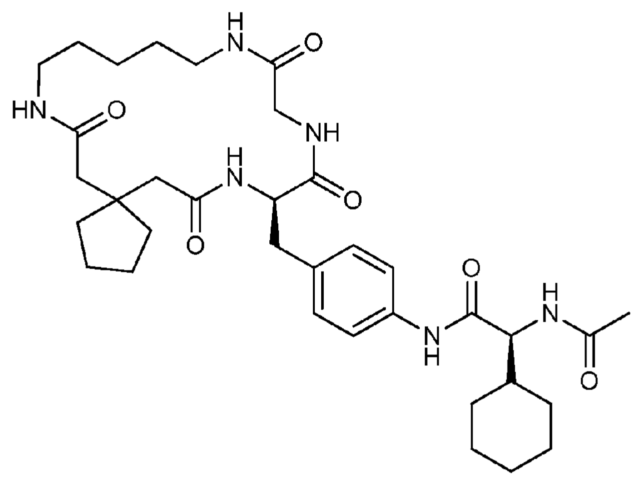
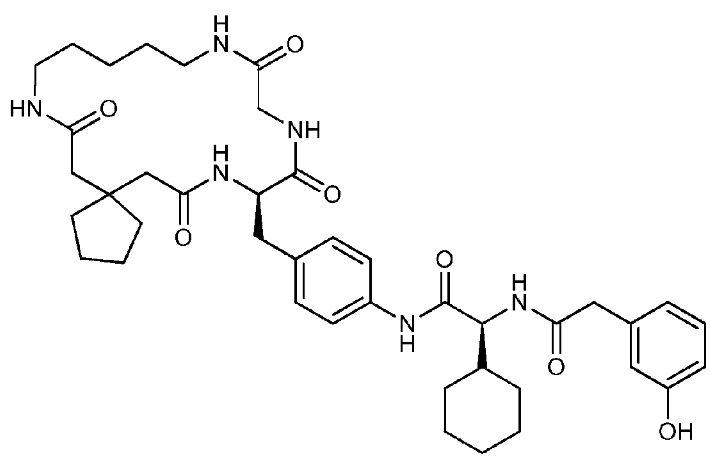
Compound No.	Structure
377	
378	

FIG. 12-124

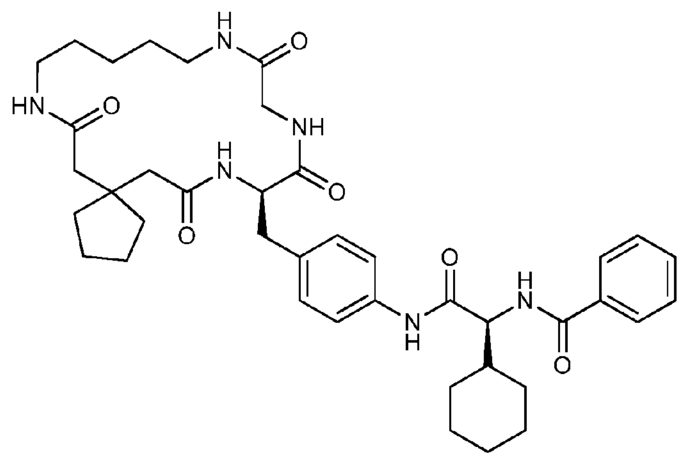
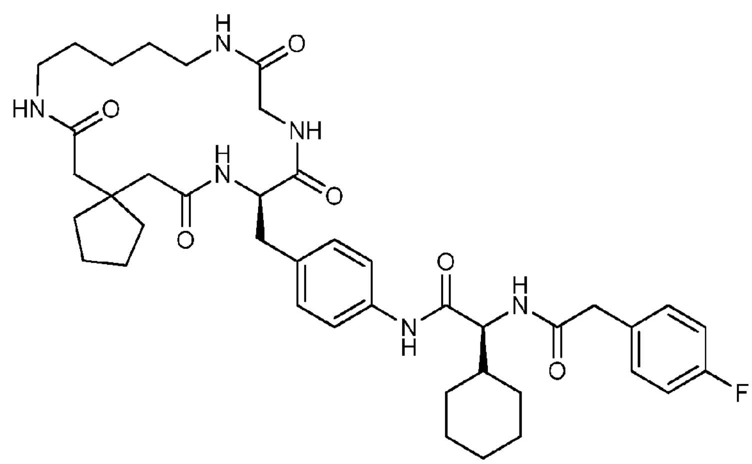
Compound No.	Structure
379	
380	

FIG. 12-125

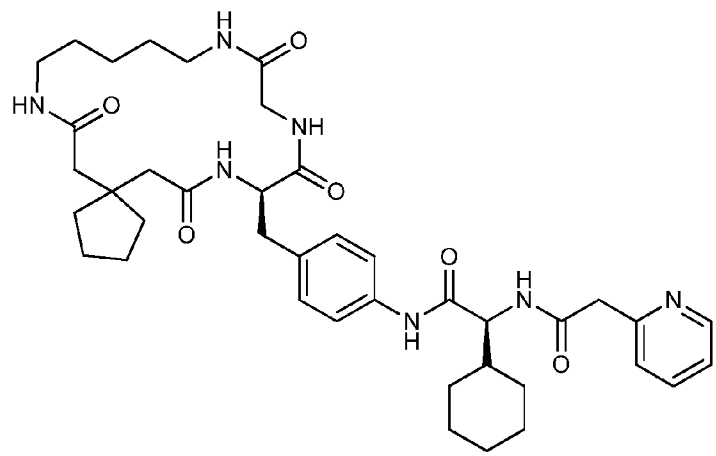
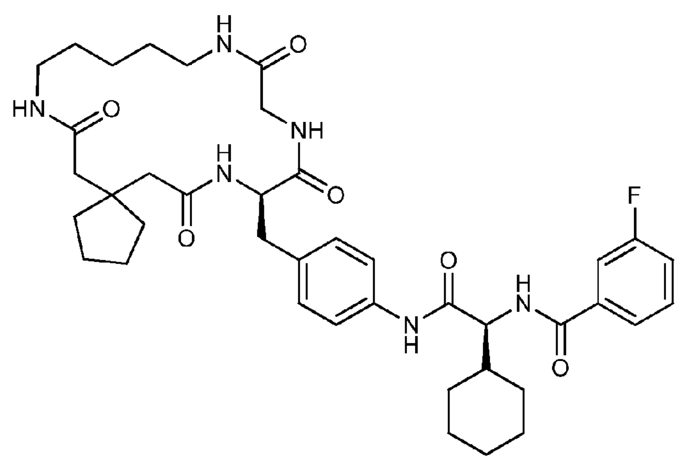
Compound No.	Structure
381	
382	

FIG. 12-126

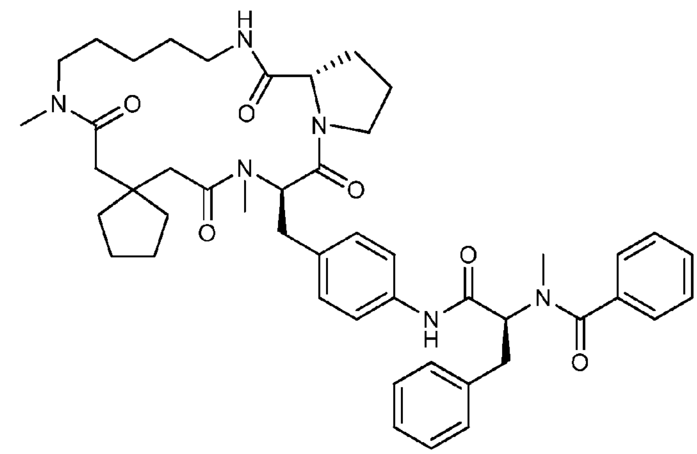
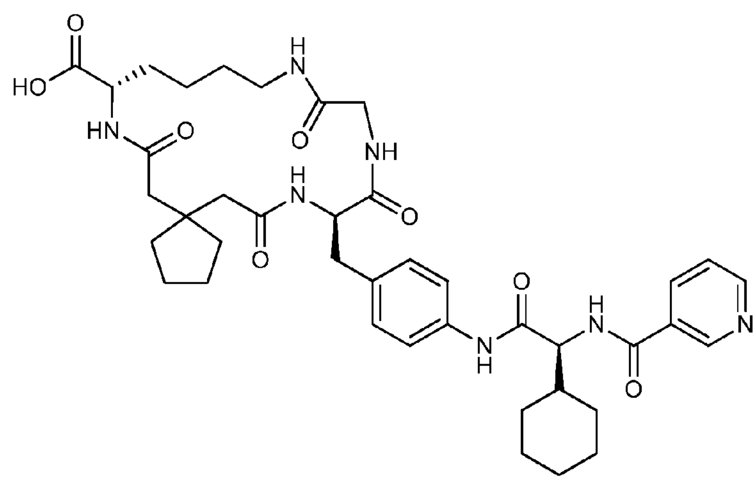
Compound No.	Structure
383	
384	

FIG. 12-127

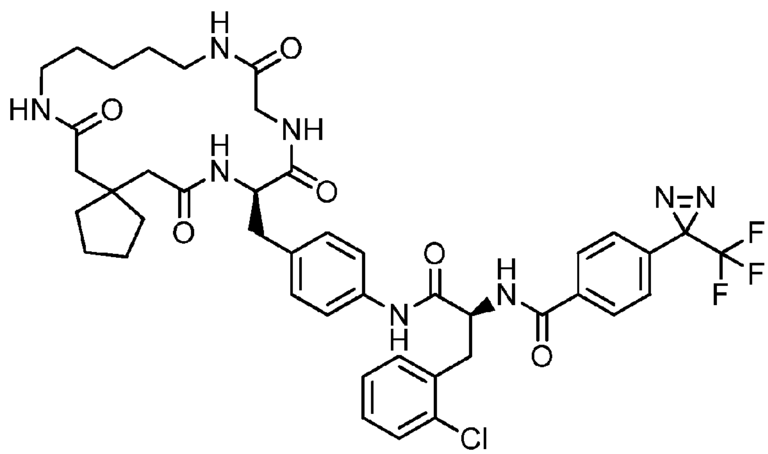
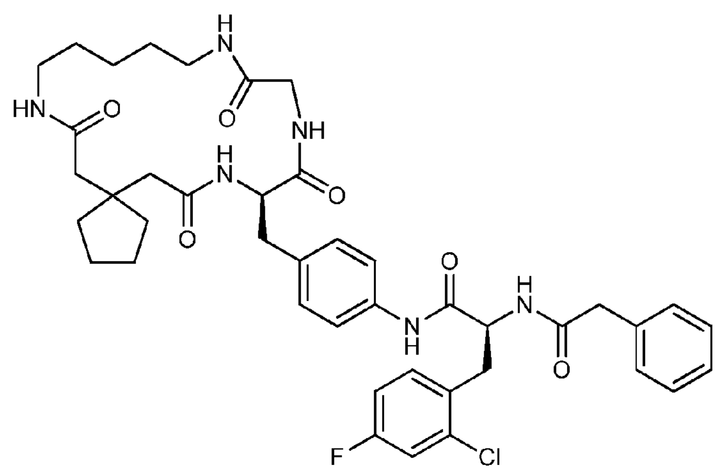
Compound No.	Structure
385	
386	

FIG. 12-128

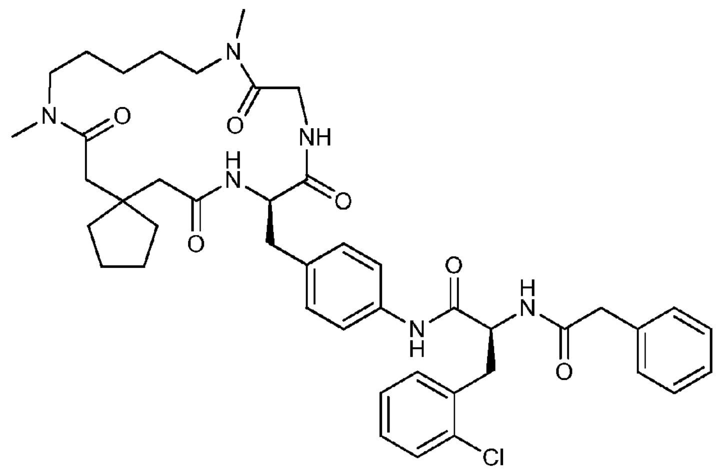
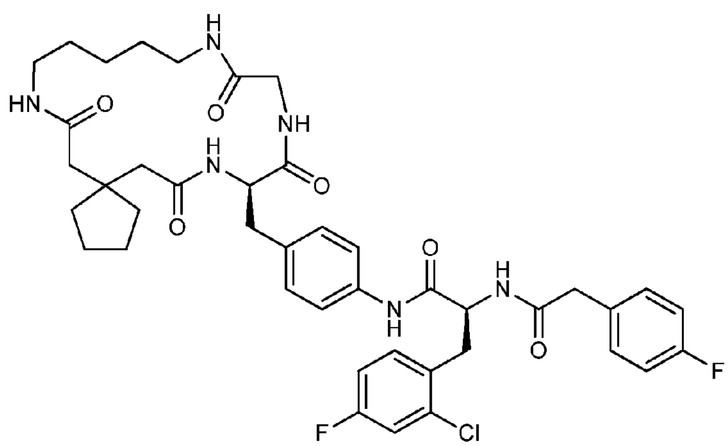
Compound No.	Structure
387	
388	

FIG. 12-129

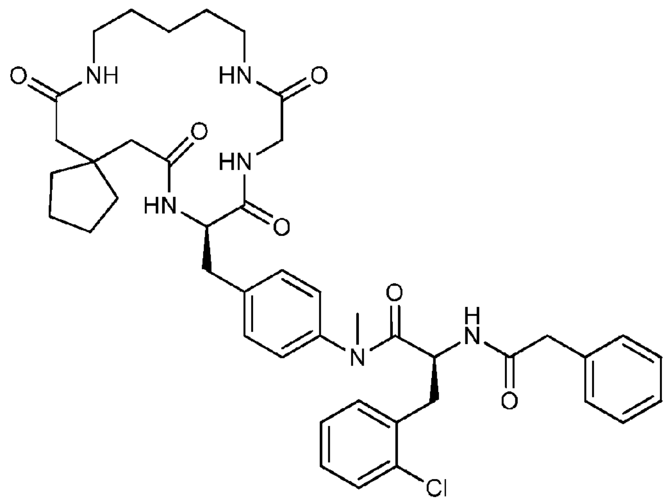
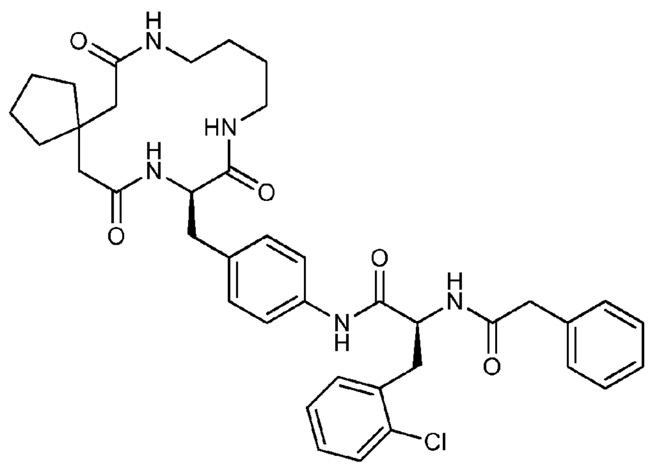
Compound No.	Structure
390	
391	

FIG. 12-130

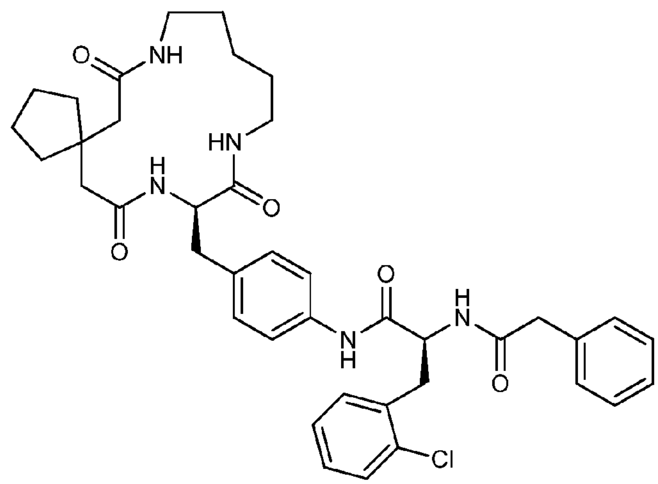
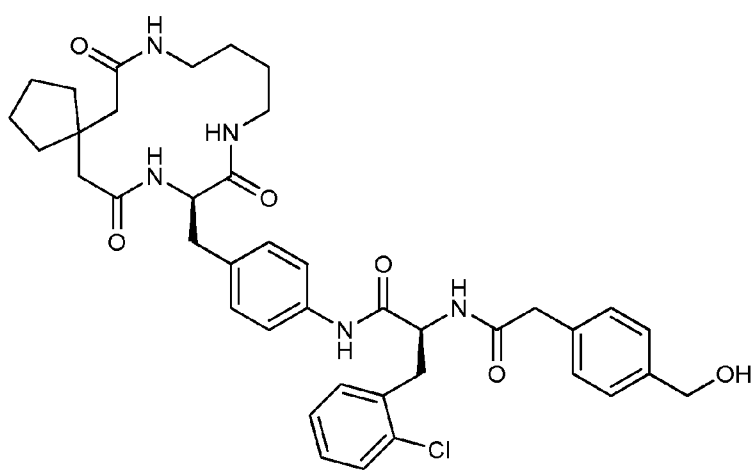
Compound No.	Structure
392	
393	

FIG. 12-131

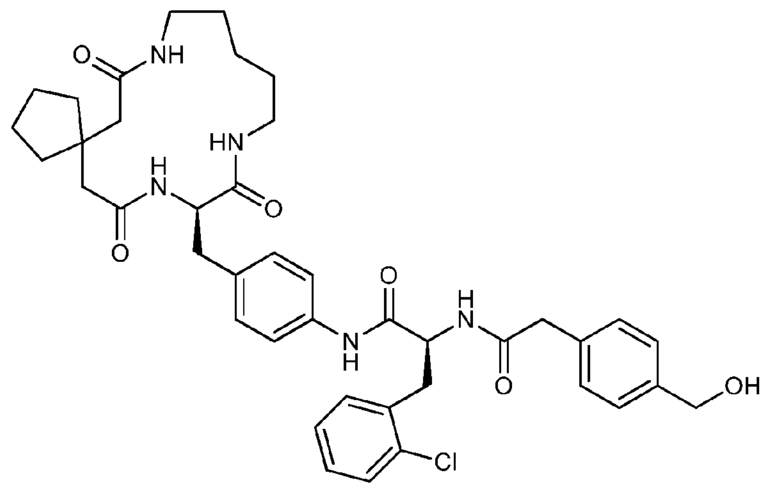
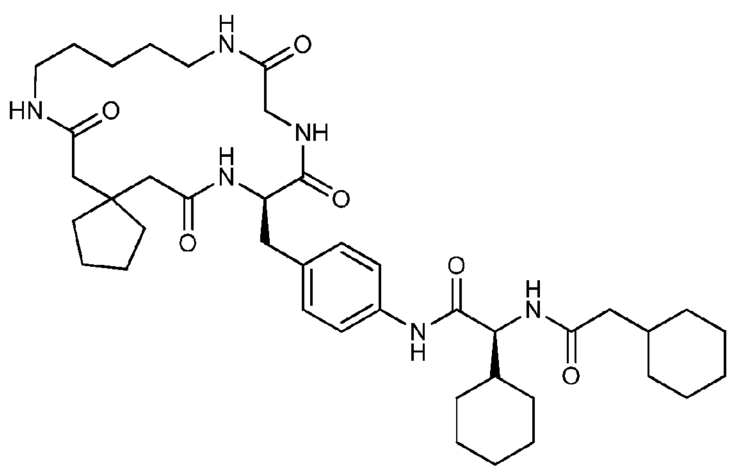
Compound No.	Structure
394	
395	

FIG. 12-132

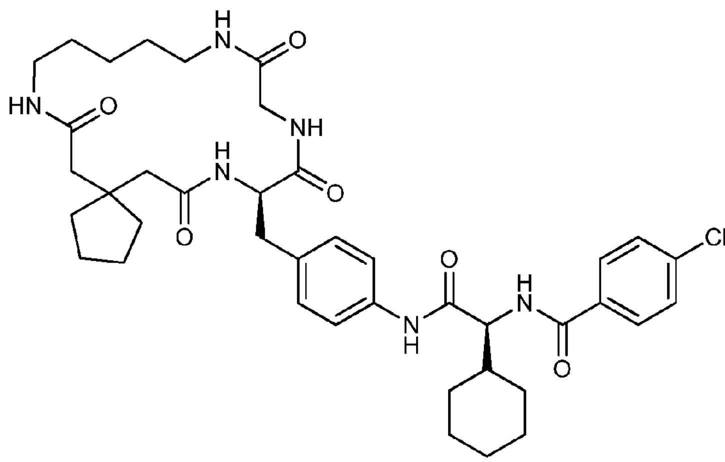
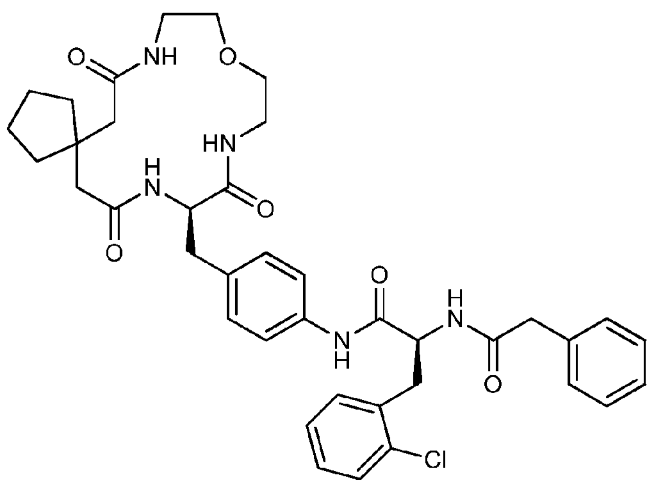
Compound No.	Structure
396	
397	

FIG. 12-133

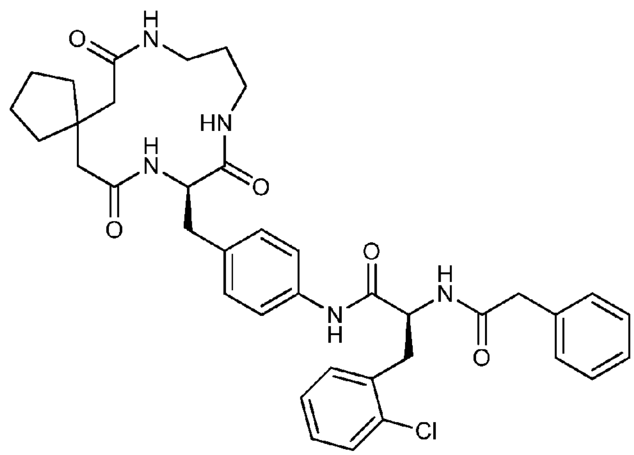
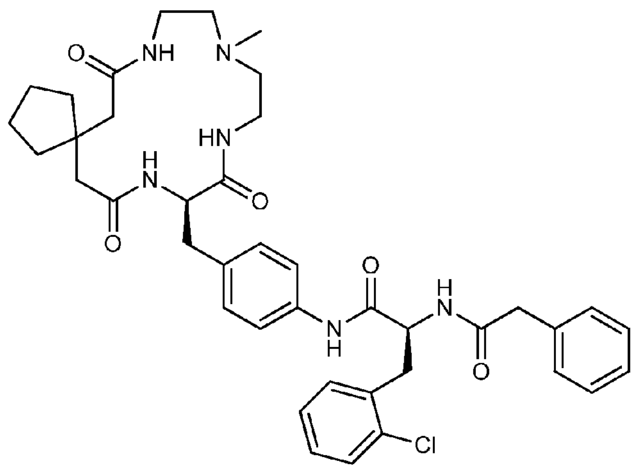
Compound No.	Structure
398	
399	

FIG. 12-134

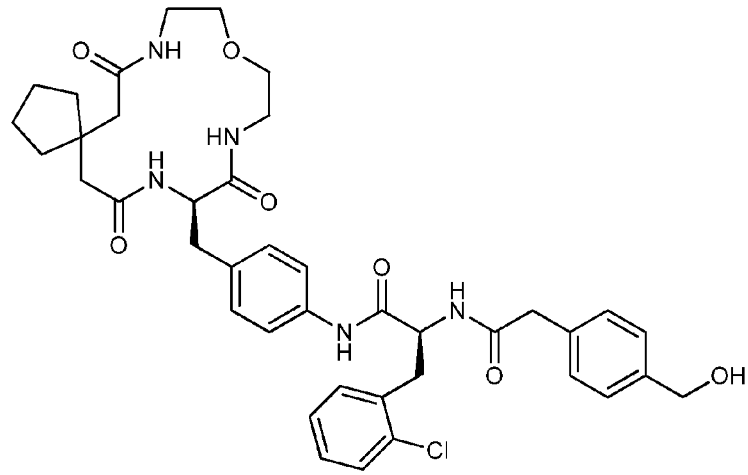
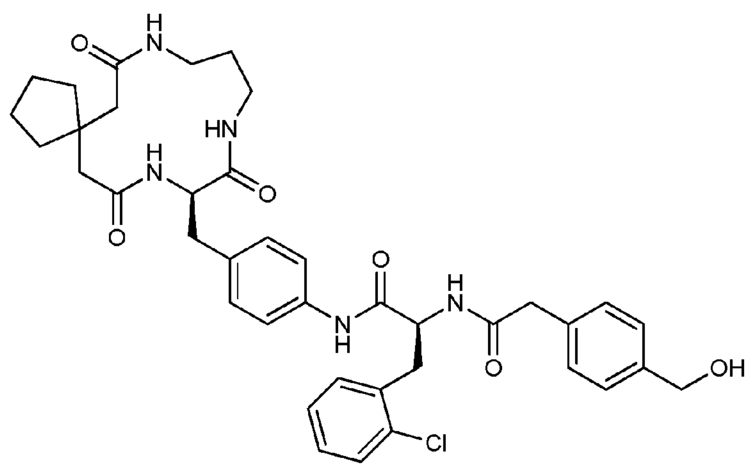
Compound No.	Structure
400	
401	

FIG. 12-135

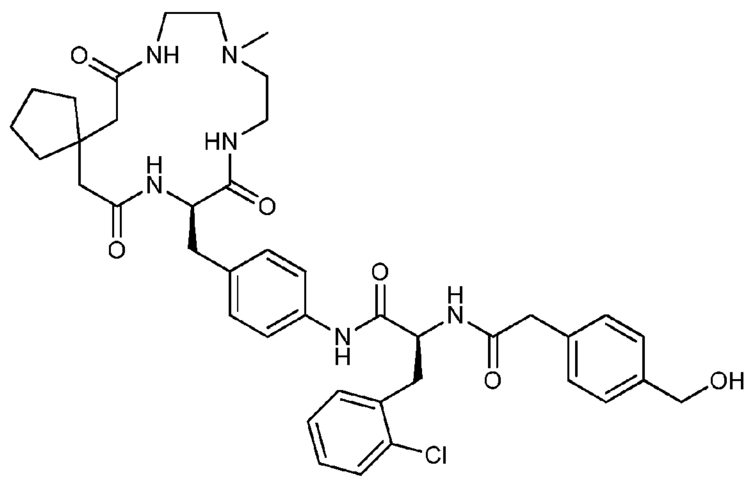
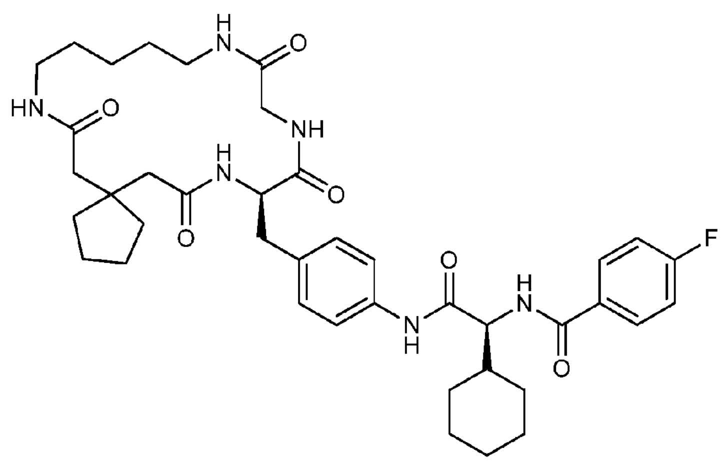
Compound No.	Structure
402	
403	

FIG. 12-136

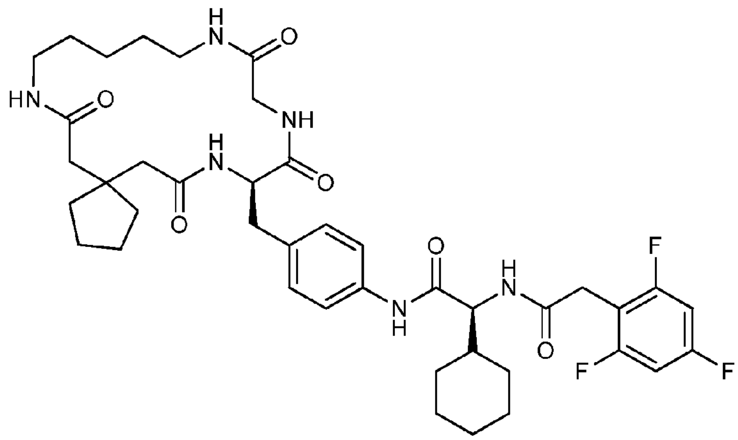
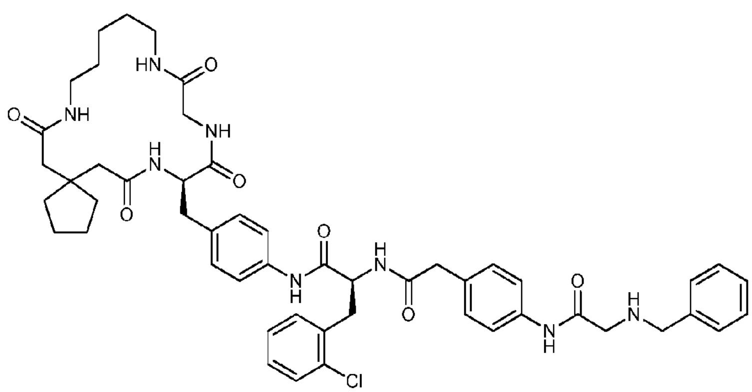
Compound No.	Structure
404	
405	

FIG. 12-137

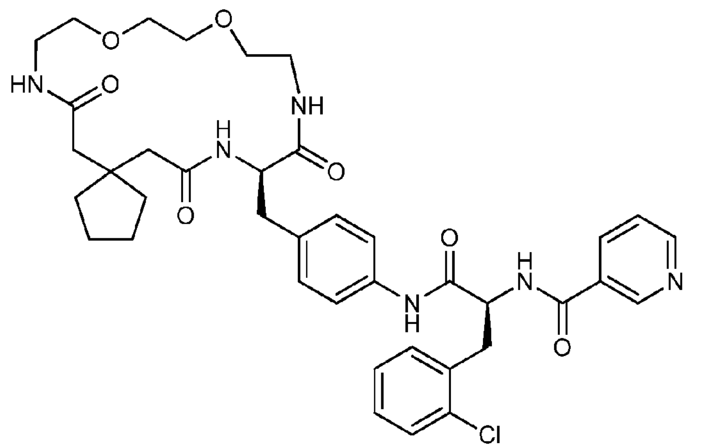
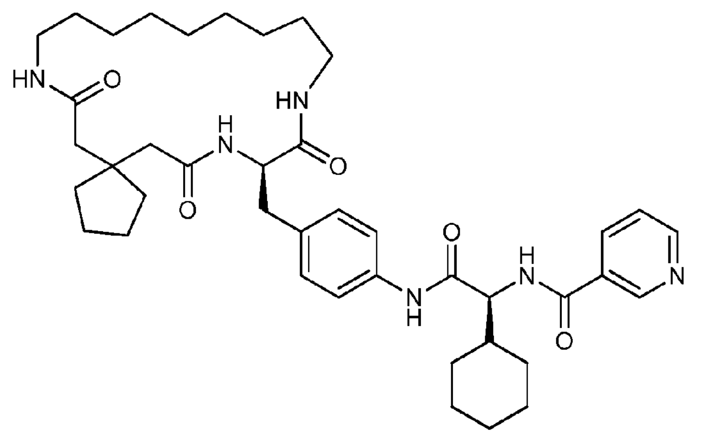
Compound No.	Structure
406	
407	

FIG. 12-138

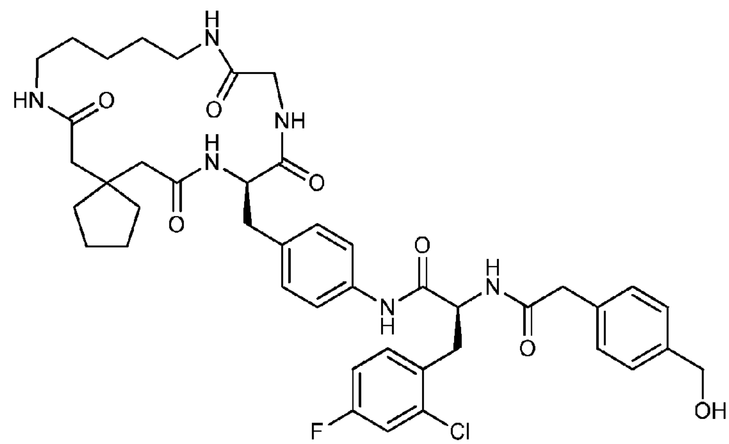
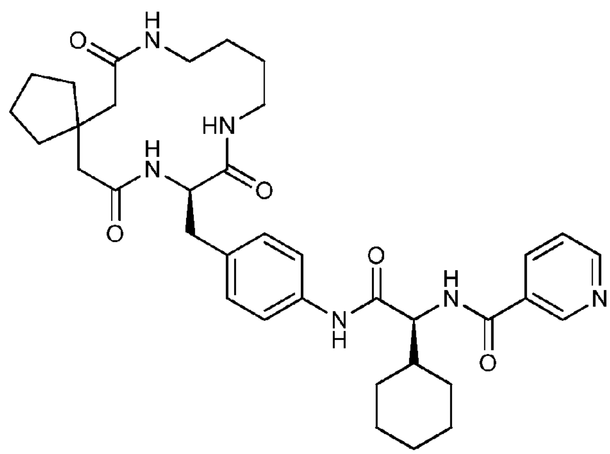
Compound No.	Structure
408	
409	

FIG. 12-139

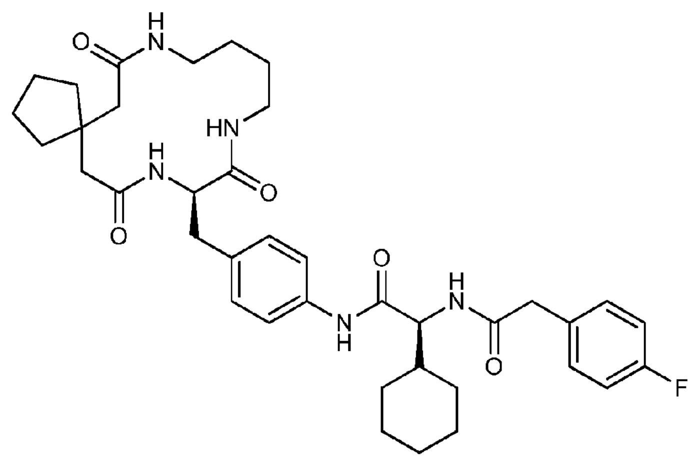
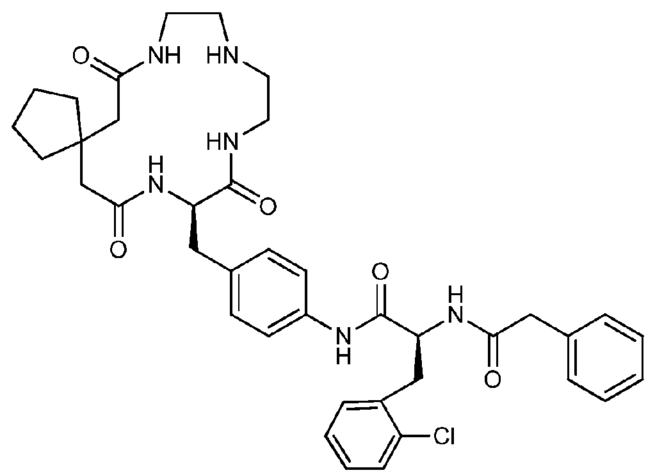
Compound No.	Structure
410	
411	

FIG. 12-140

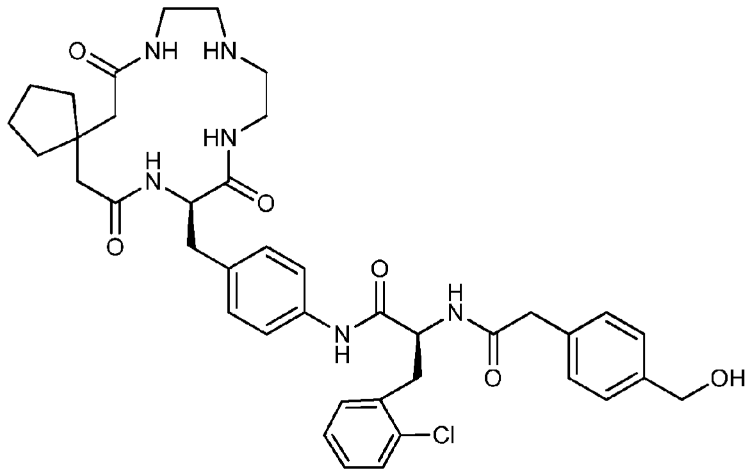
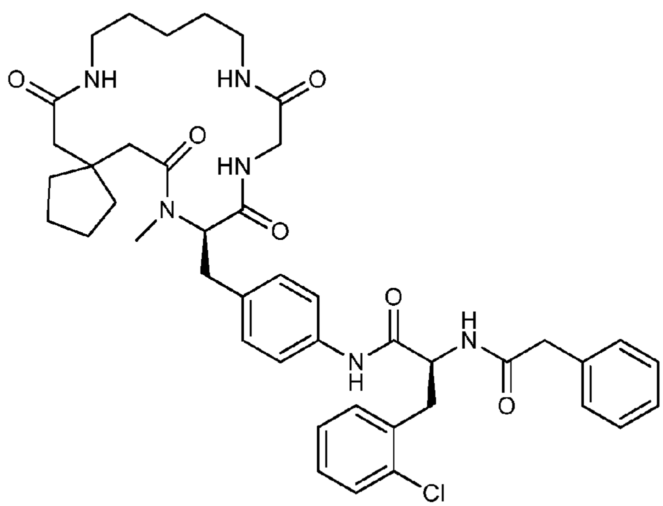
Compound No.	Structure
412	
413	

FIG. 12-141

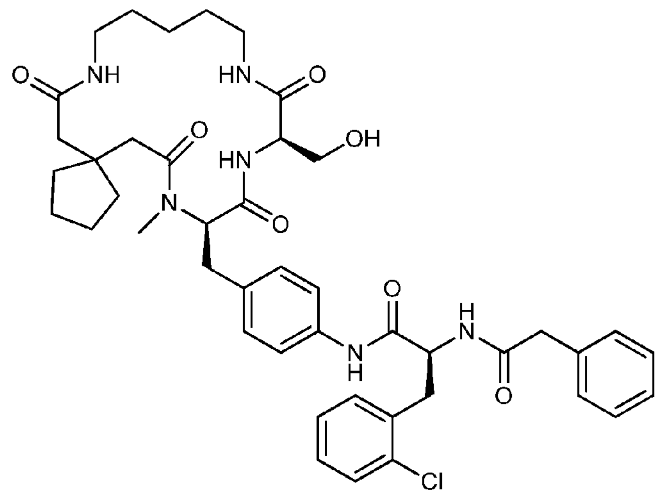
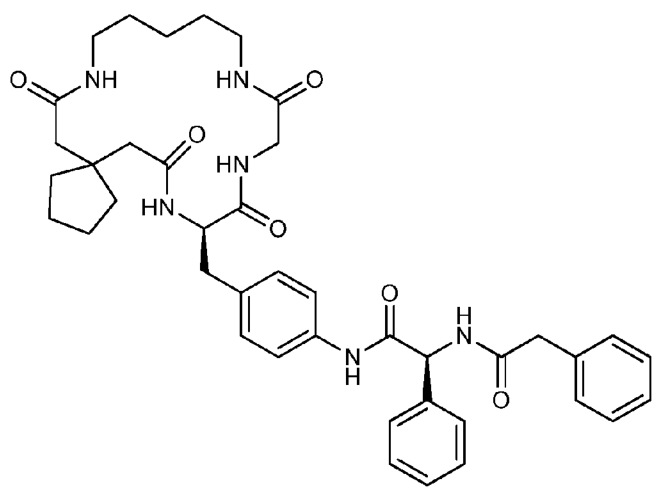
Compound No.	Structure
414	
415	

FIG. 12-142

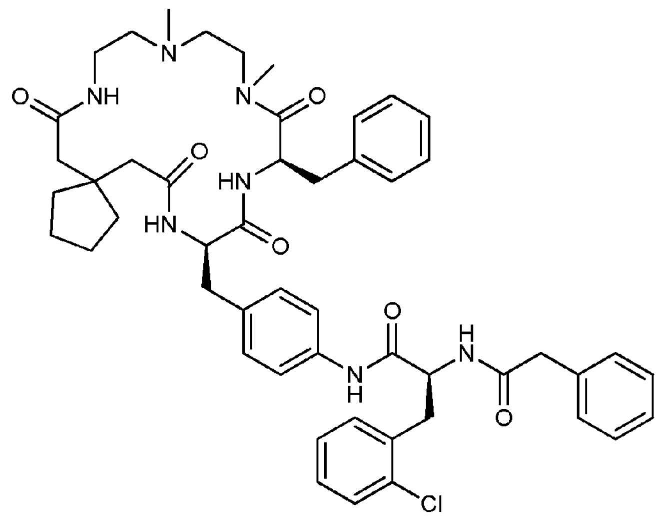
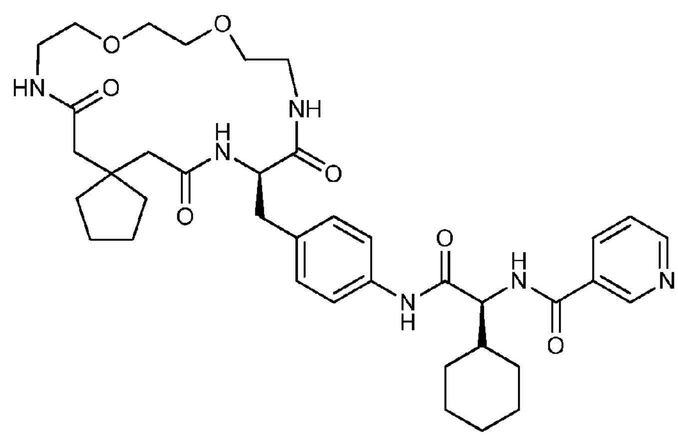
Compound No.	Structure
416	
417	

FIG. 12-143

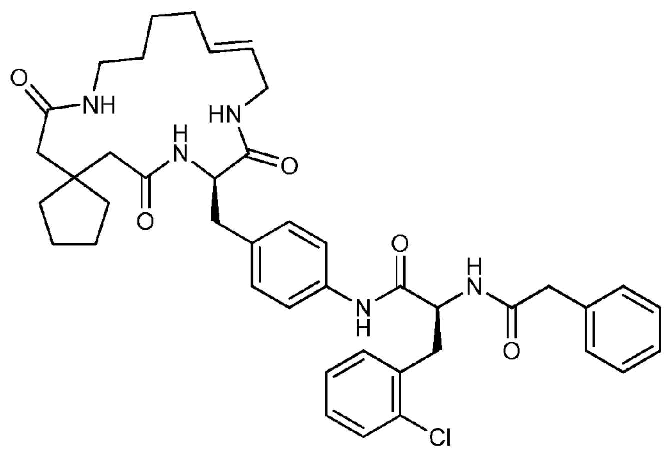
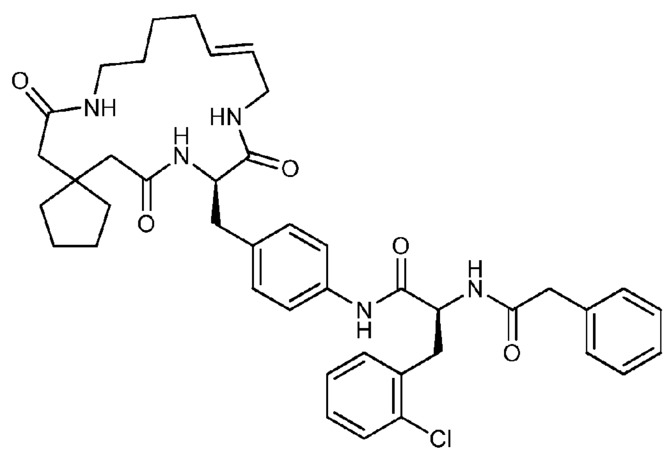
Compound No.	Structure
418	
419	

FIG. 12-144

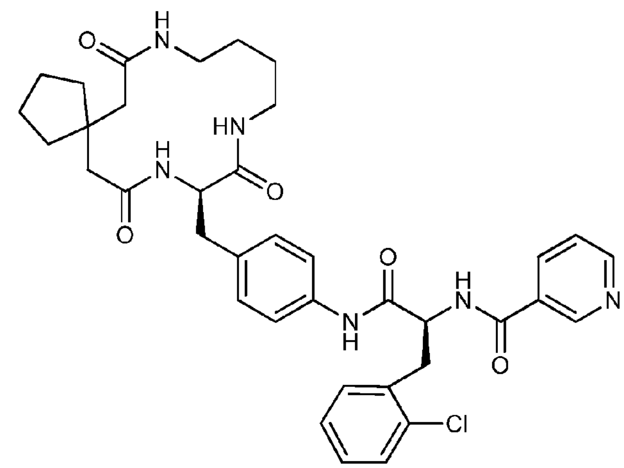
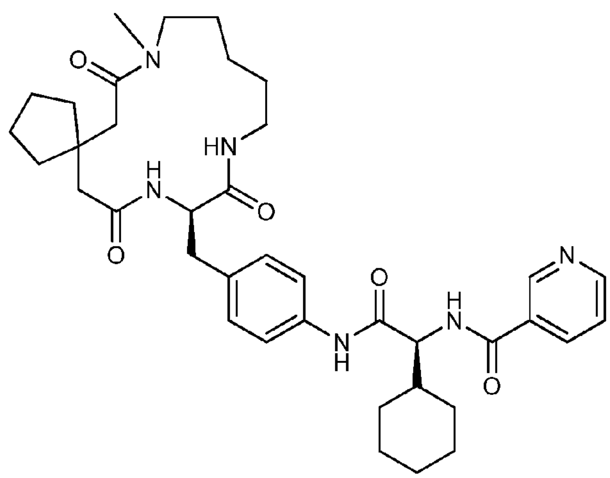
Compound No.	Structure
420	
421	

FIG. 12-145

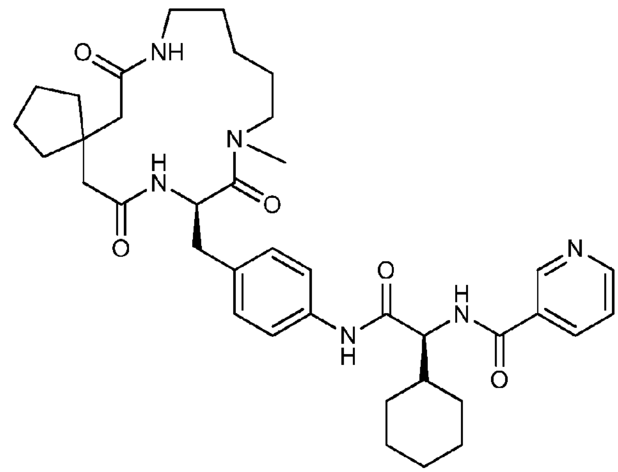
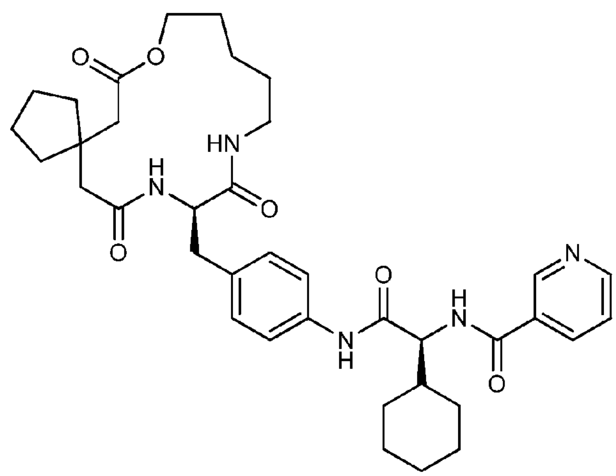
Compound No.	Structure
422	
423	

FIG. 12-146

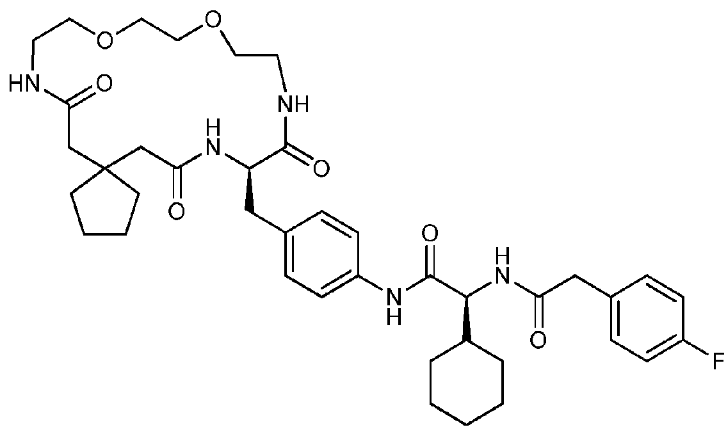
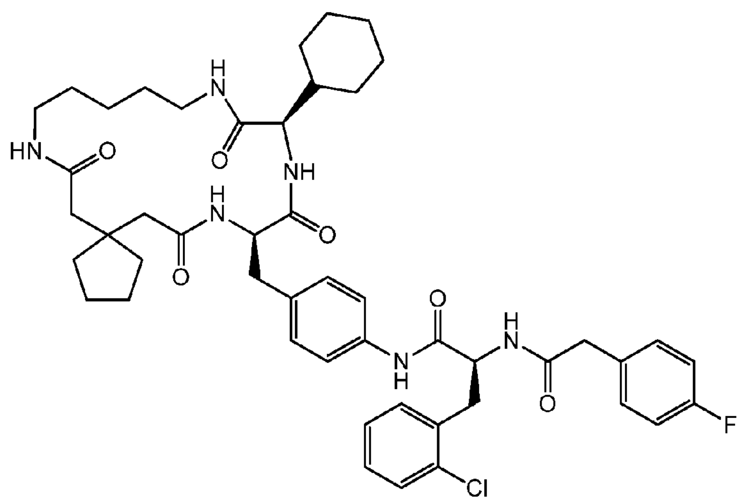
Compound No.	Structure
424	
425	

FIG. 12-147

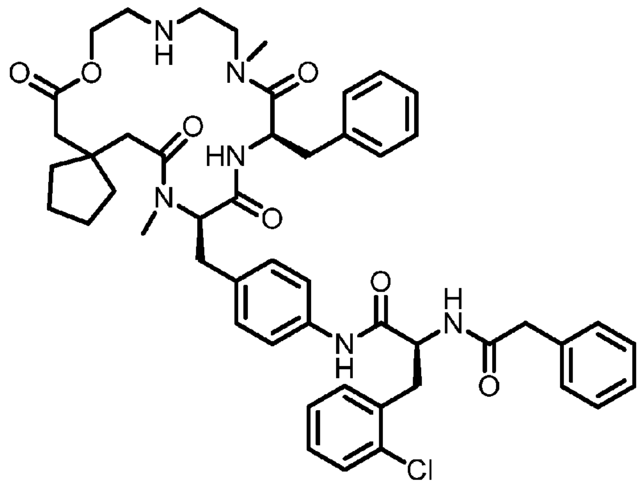
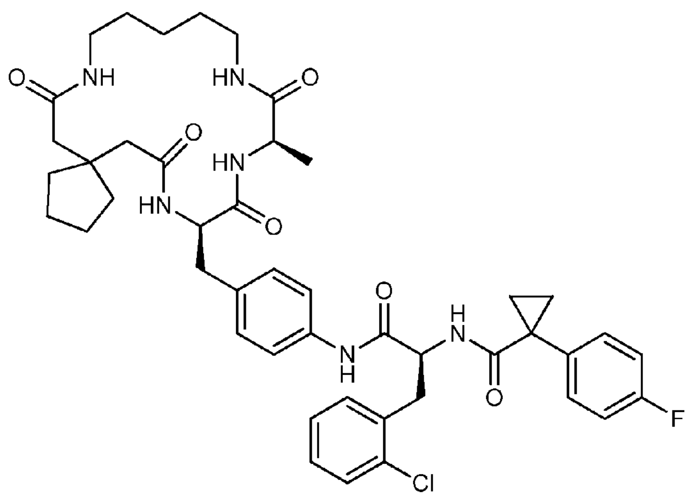
Compound No.	Structure
426	
427	

FIG. 12-148

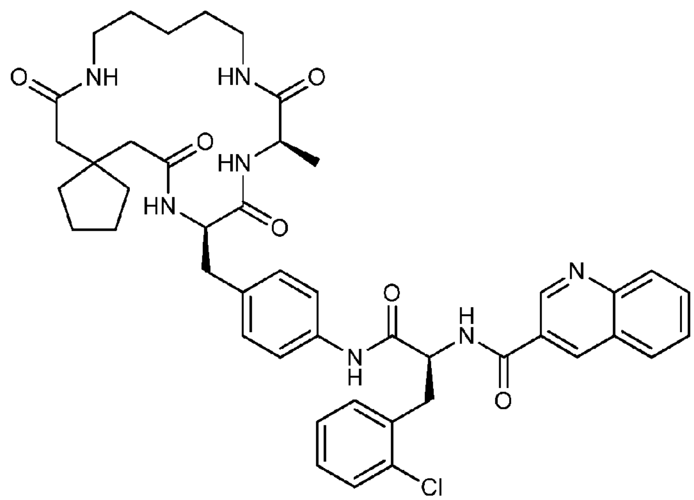
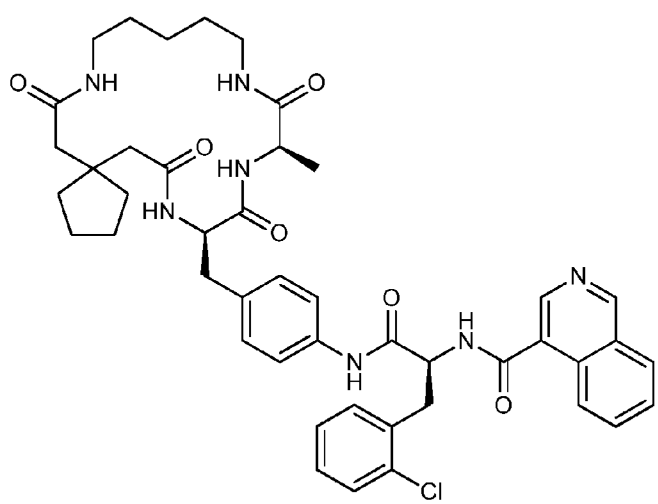
Compound No.	Structure
428	
429	

FIG. 12-149

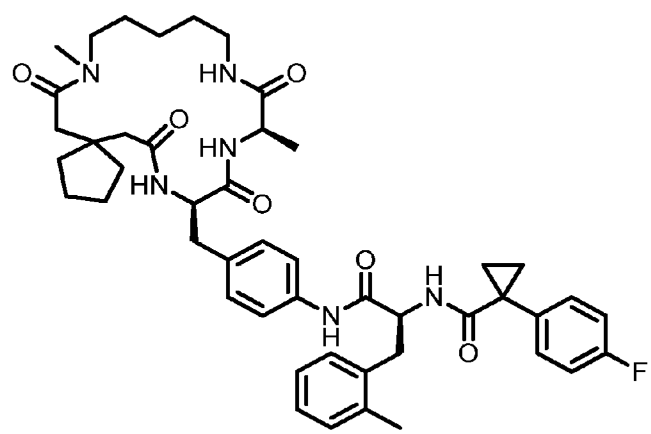
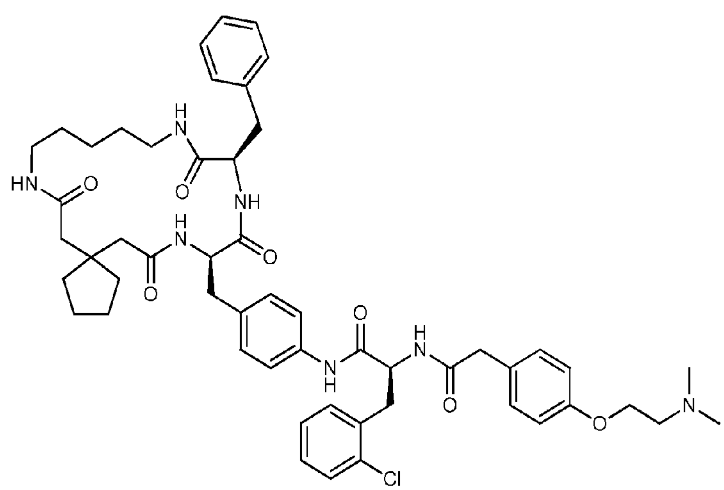
Compound No.	Structure
430	
431	

FIG. 12-150

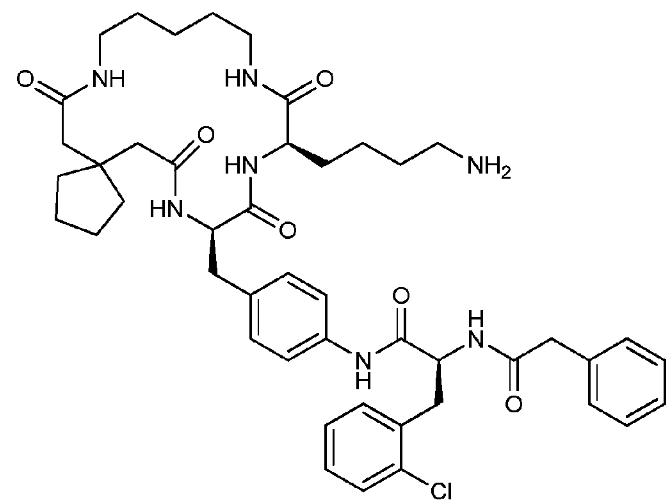
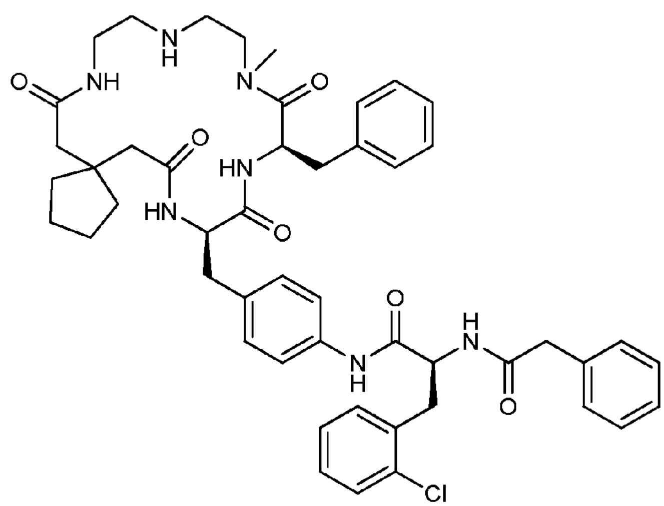
Compound No.	Structure
432	
433	

FIG. 12-151

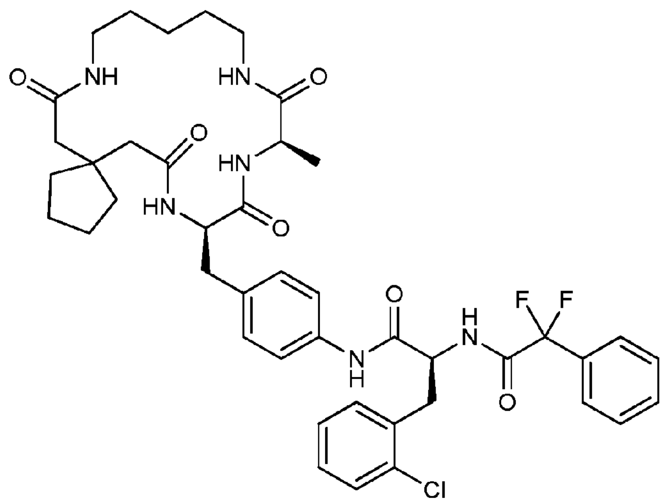
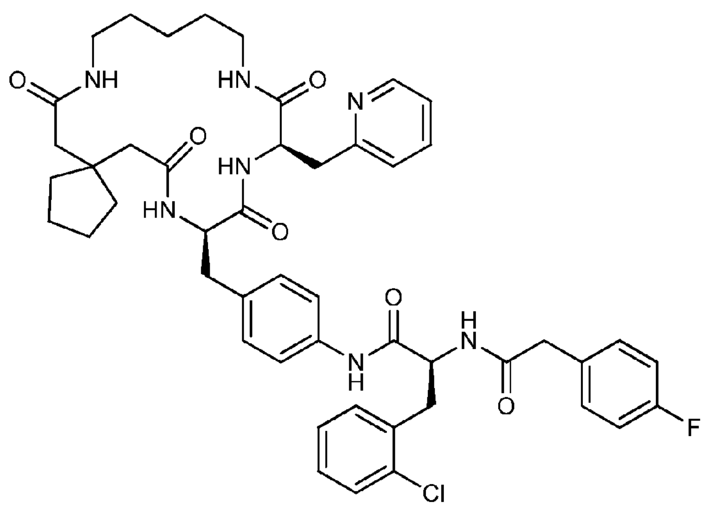
Compound No.	Structure
434	
435	

FIG. 12-152

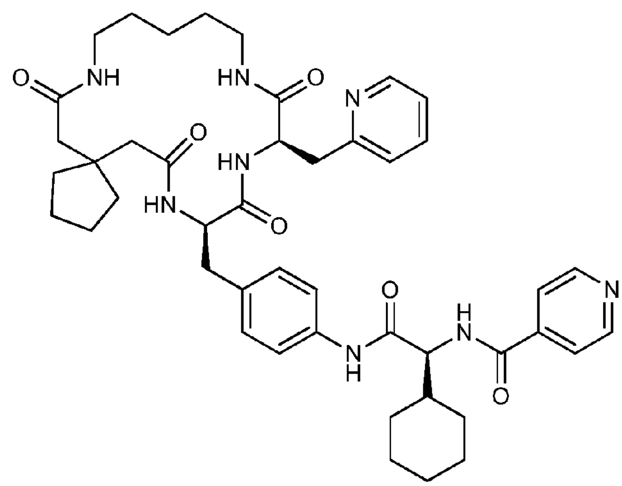
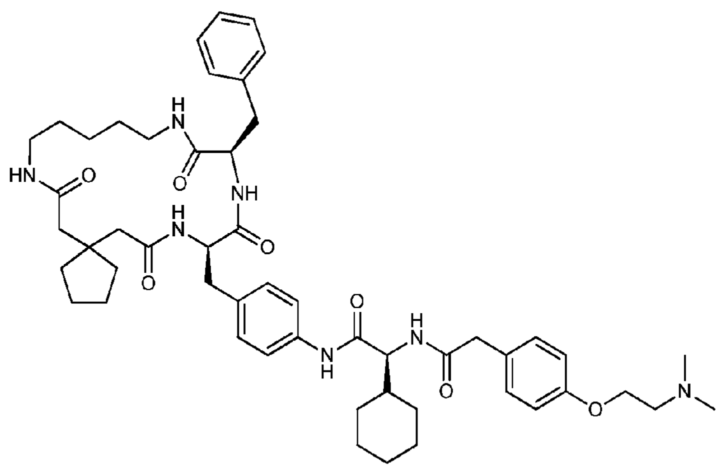
Compound No.	Structure
436	
437	

FIG. 12-153

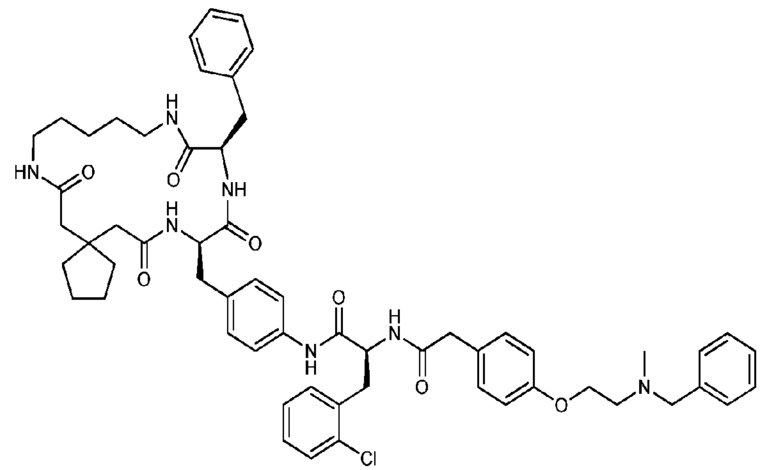
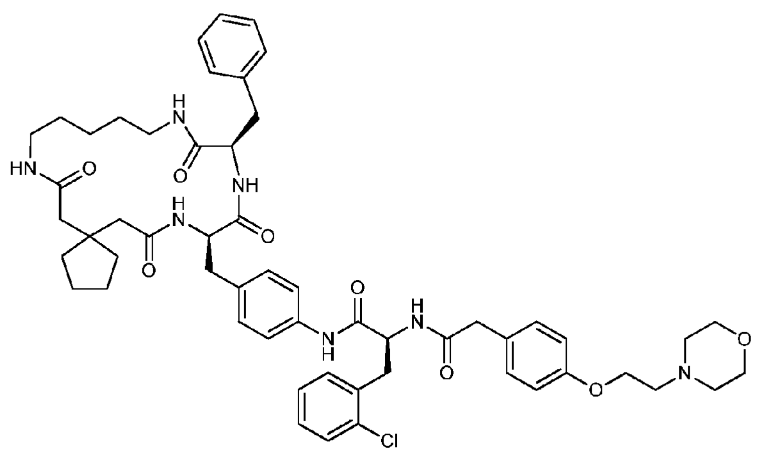
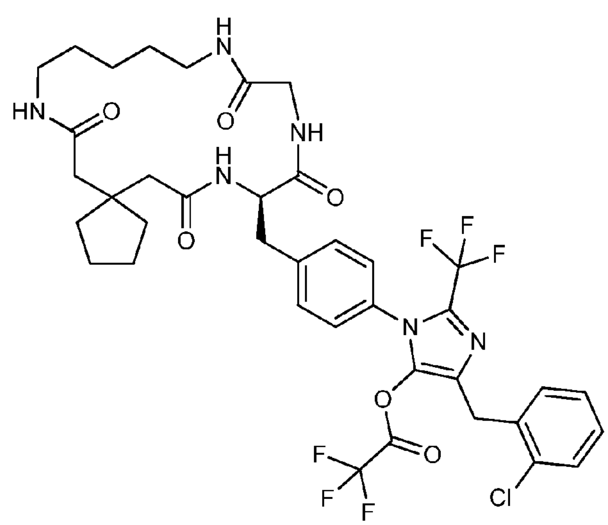
Compound No.	Structure
438	
439	
440	

FIG. 12-154

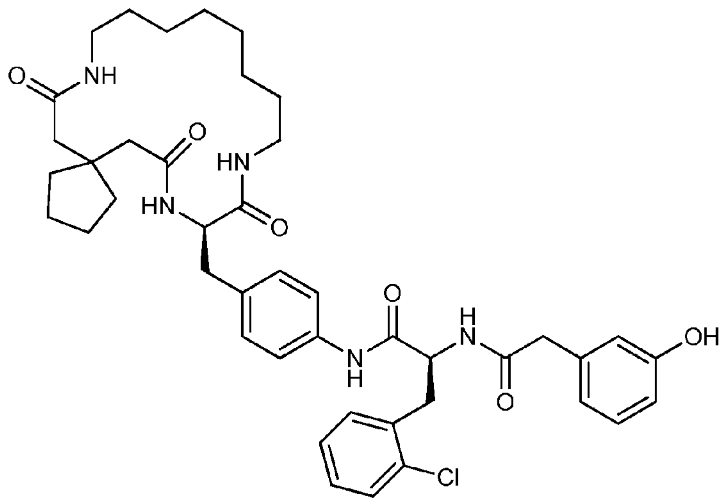
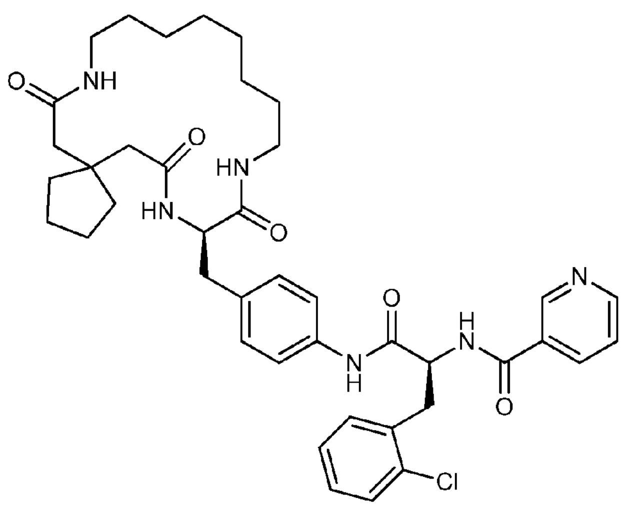
Compound No.	Structure
441	
442	

FIG. 12-155

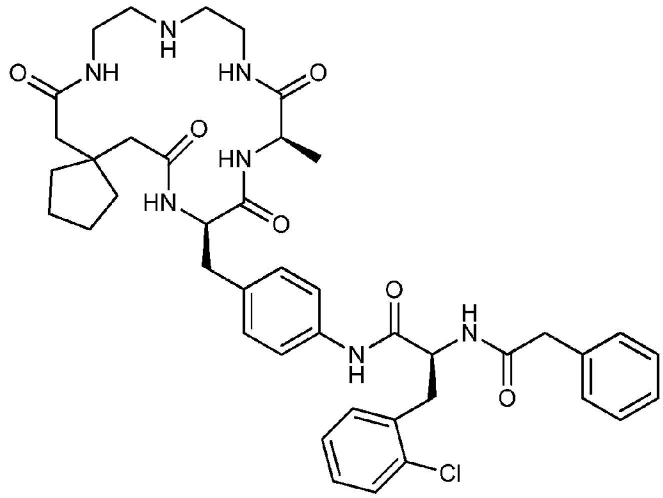
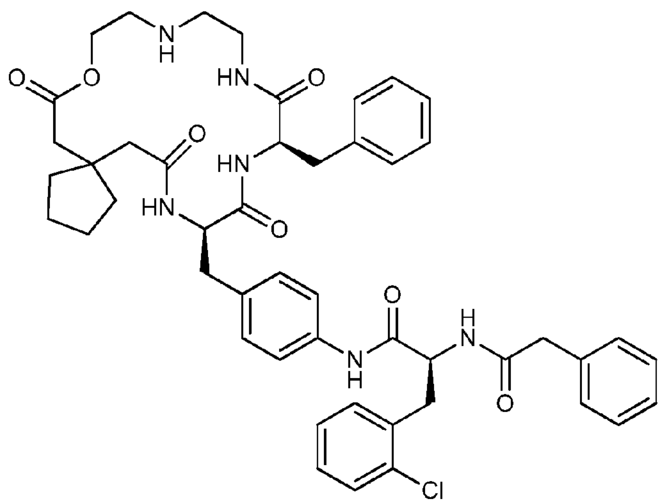
Compound No.	Structure
443	
444	

FIG. 12-156

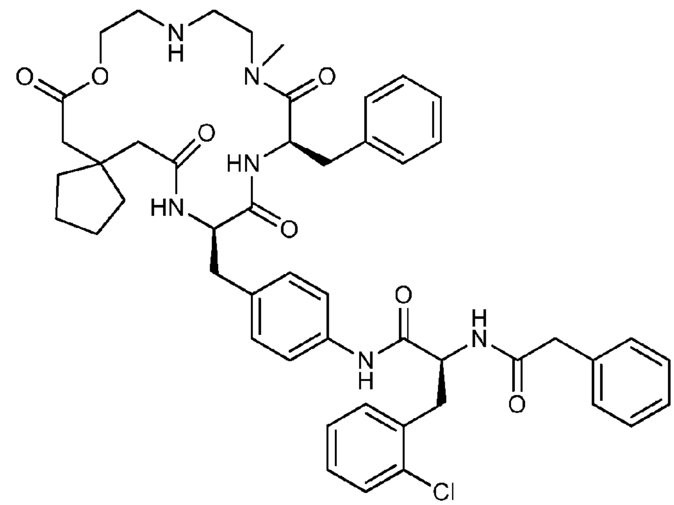
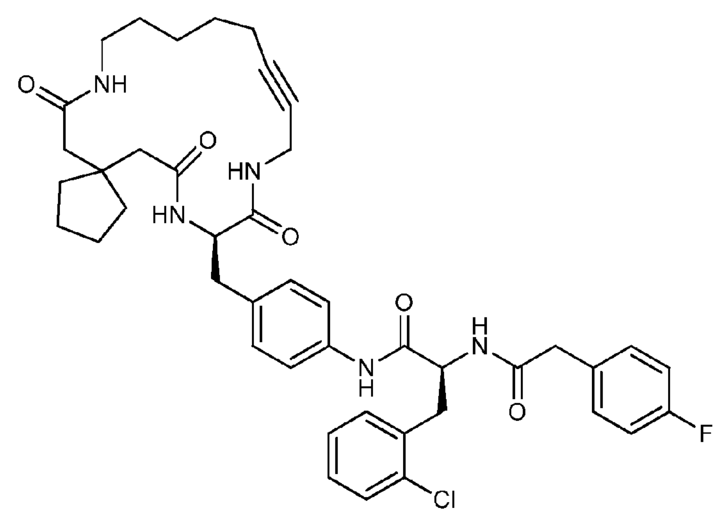
Compound No.	Structure
445	
446	

FIG. 12-157

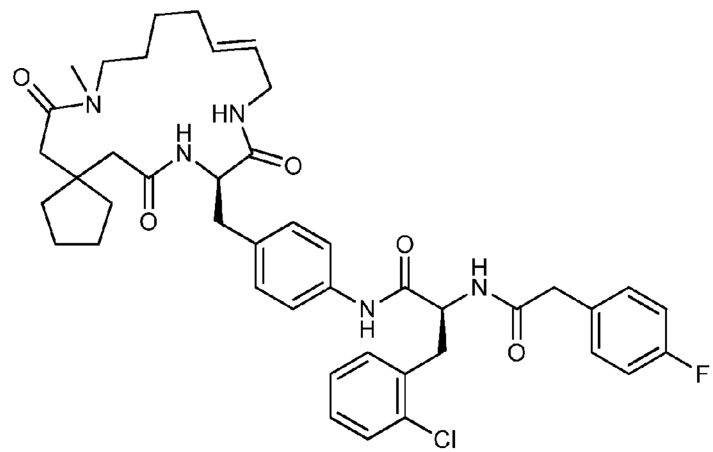
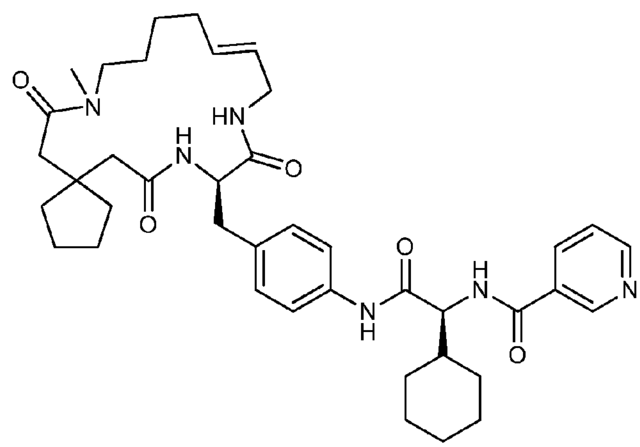
Compound No.	Structure
447	
448	

FIG. 12-158

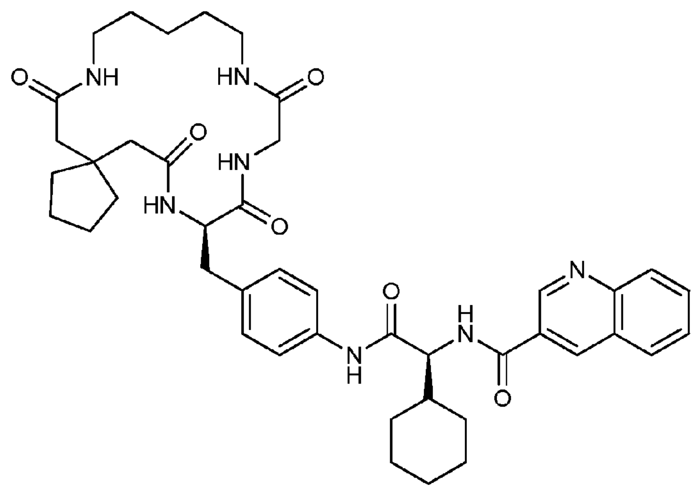
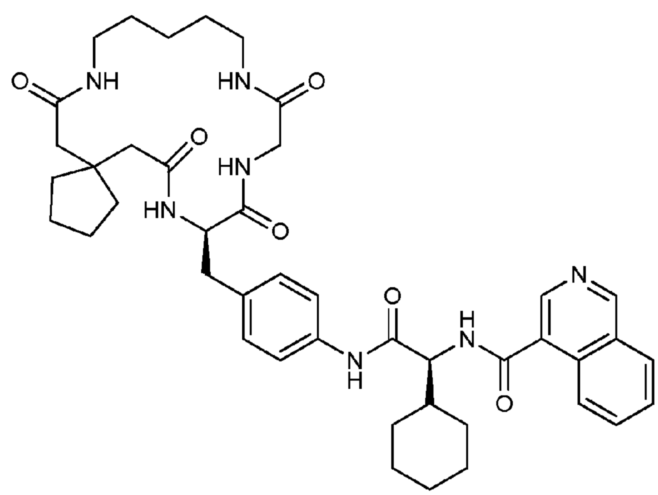
Compound No.	Structure
449	
450	

FIG. 12-159

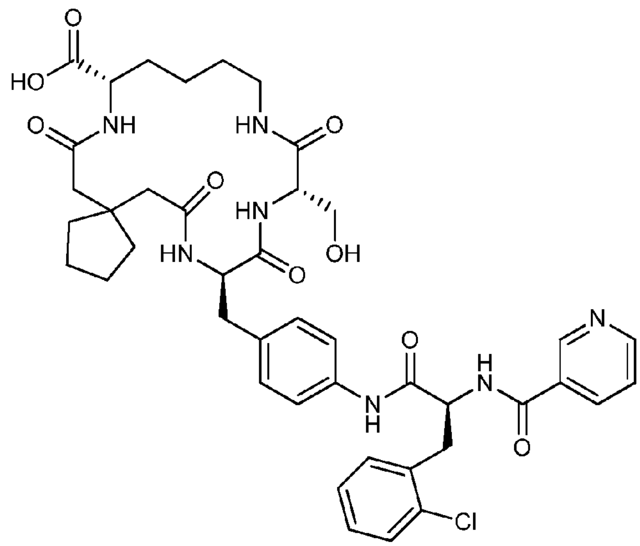
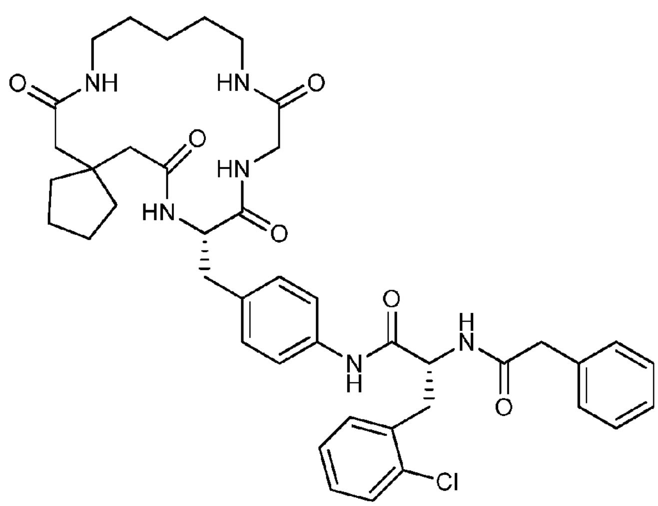
Compound No.	Structure
451	
452	

FIG. 12-160

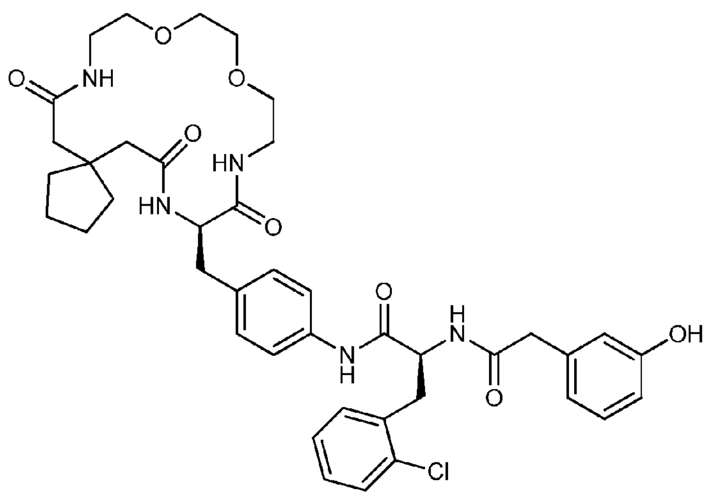
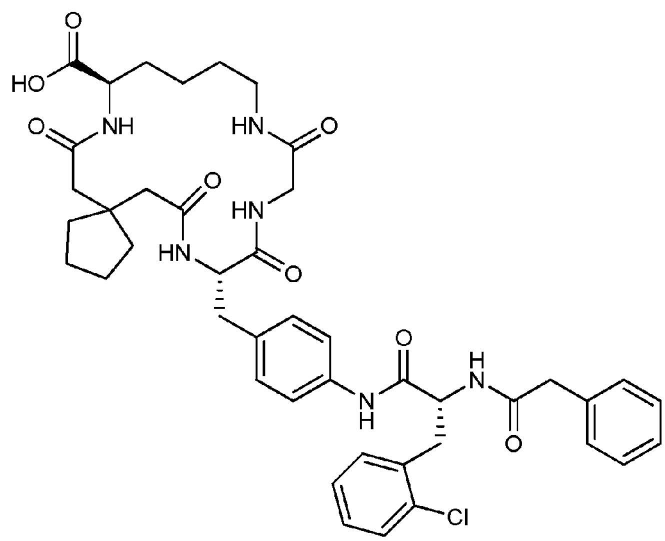
Compound No.	Structure
453	
454	

FIG. 12-161

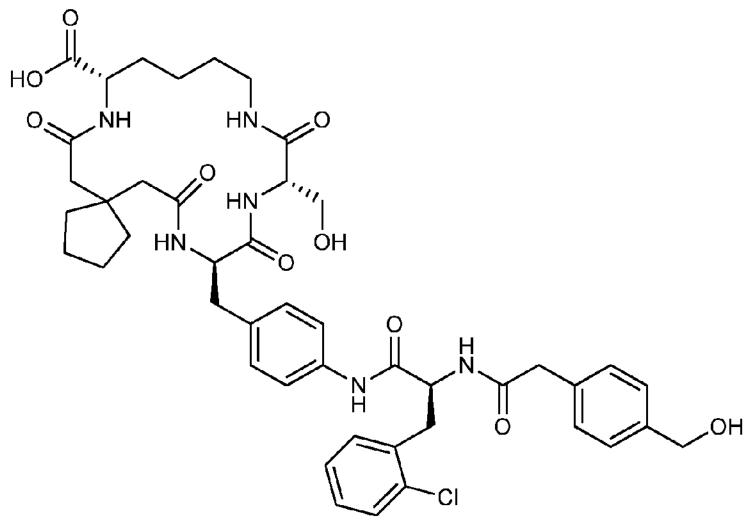
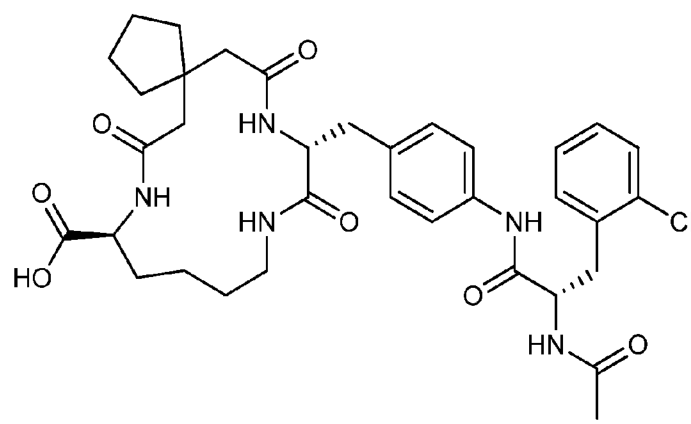
Compound No.	Structure
455	
456	

FIG. 12-162

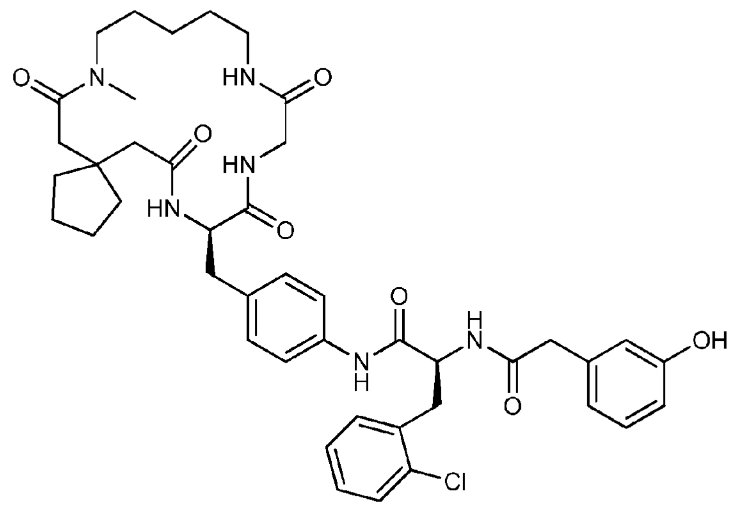
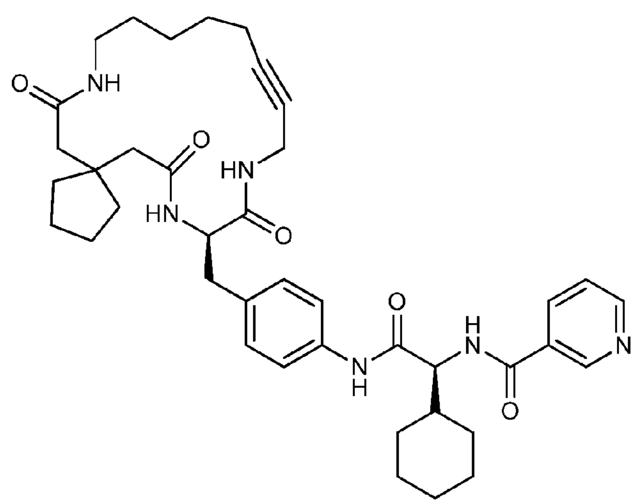
Compound No.	Structure
457	
458	

FIG. 12-163

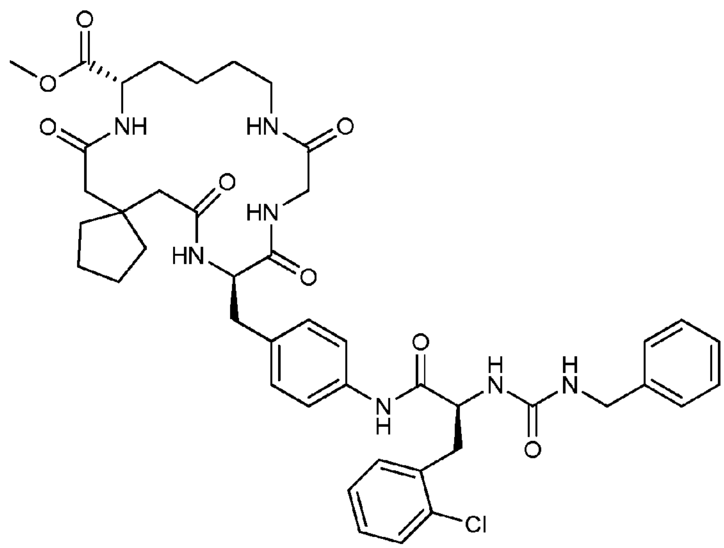
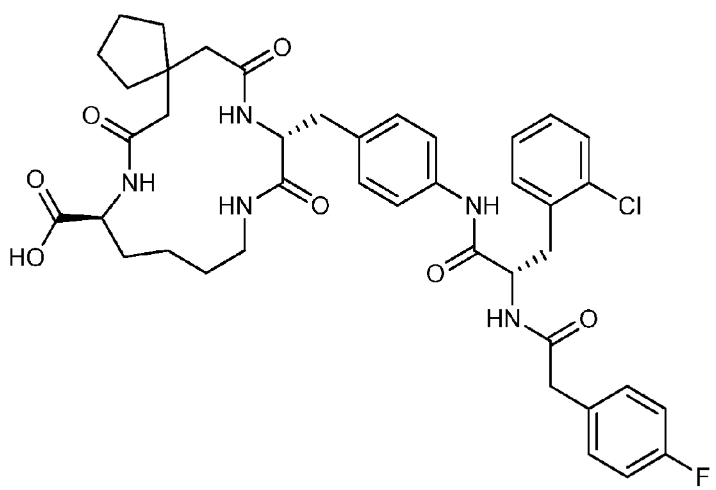
Compound No.	Structure
459	
460	

FIG. 12-164

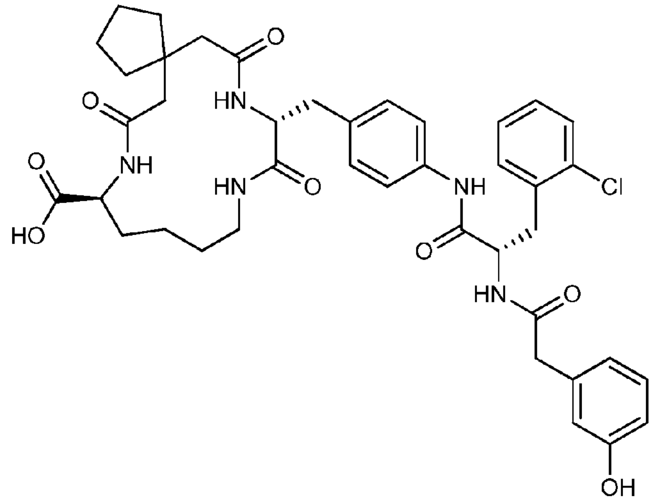
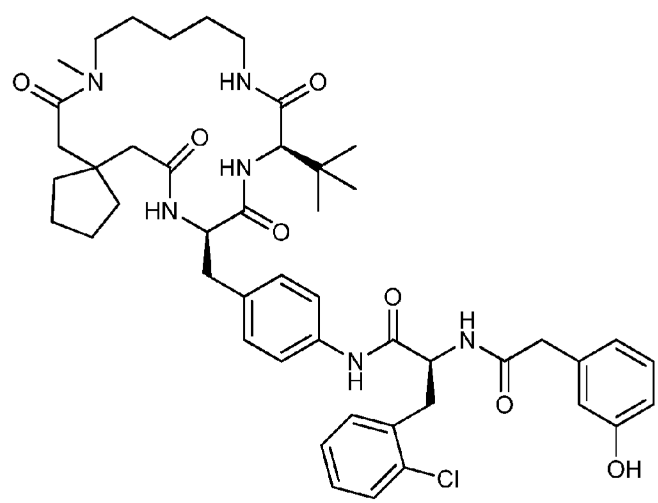
Compound No.	Structure
461	
462	

FIG. 12-165

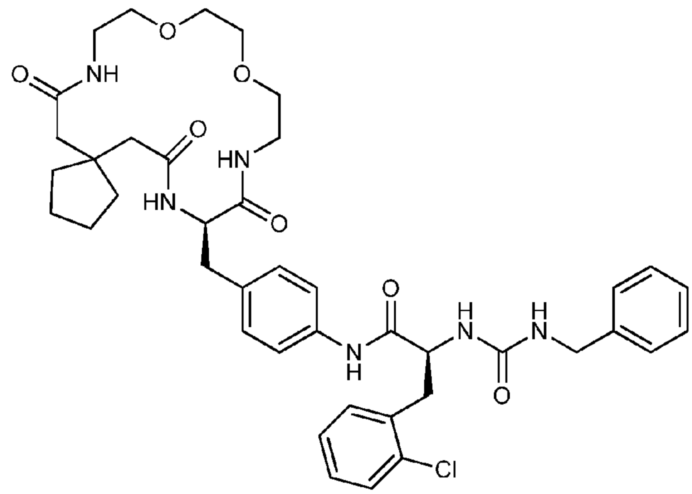
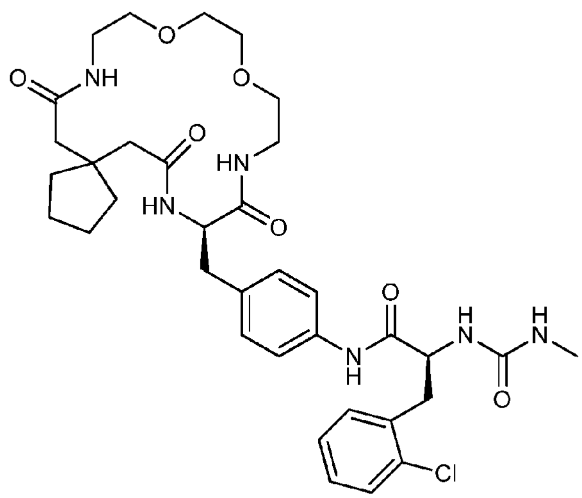
Compound No.	Structure
463	
464	

FIG. 12-166

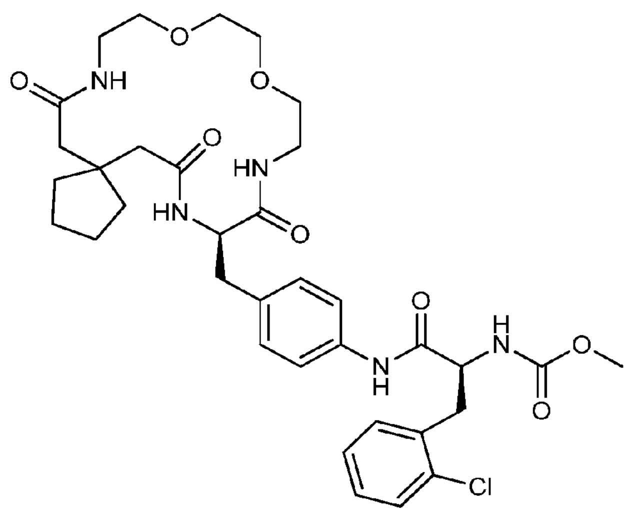
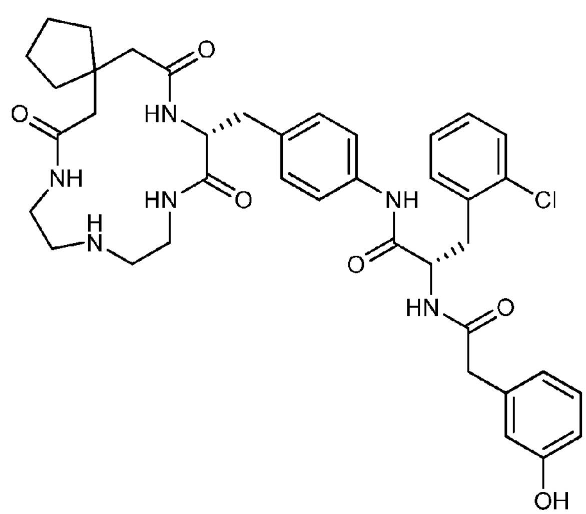
Compound No.	Structure
465	
466	

FIG. 12-167

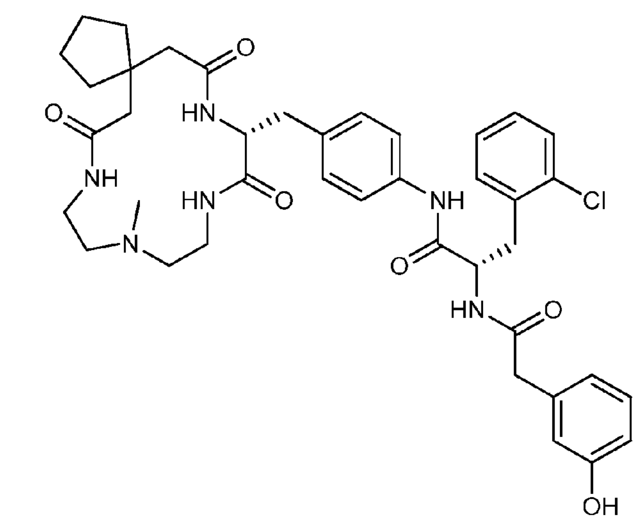
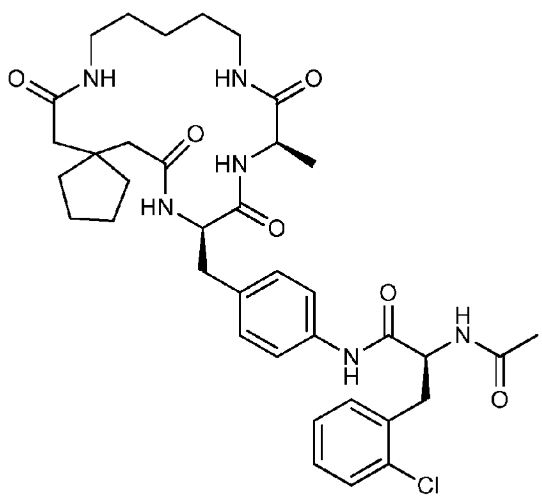
Compound No.	Structure
467	
468	

FIG. 12-168

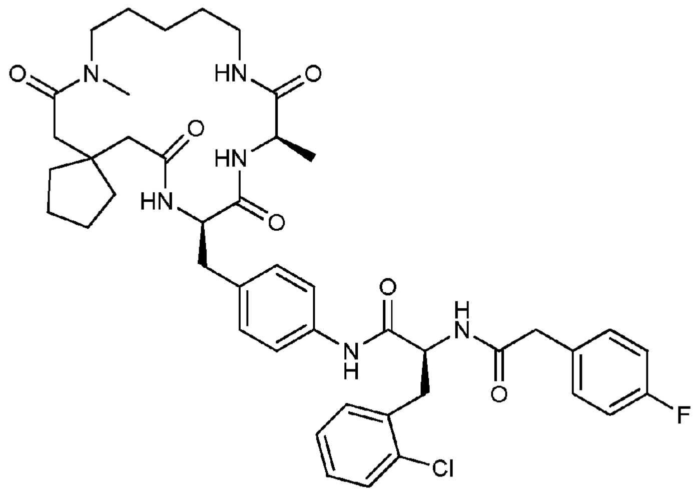
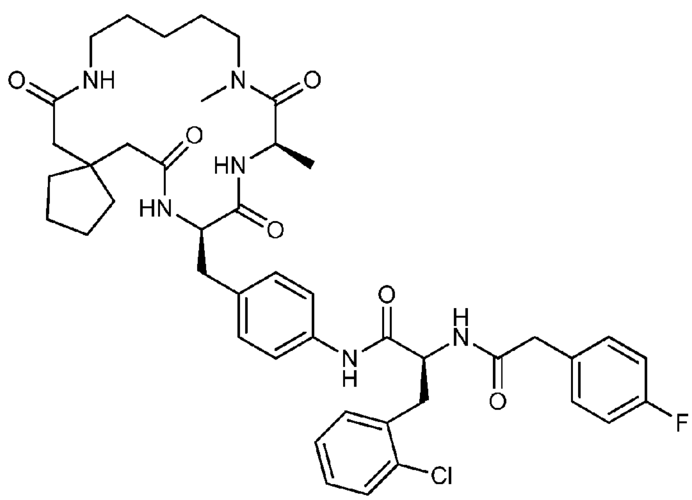
Compound No.	Structure
469	
470	

FIG. 12-169

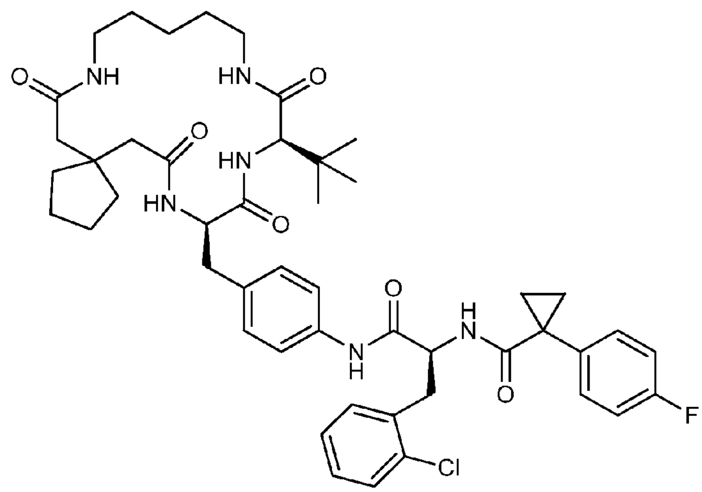
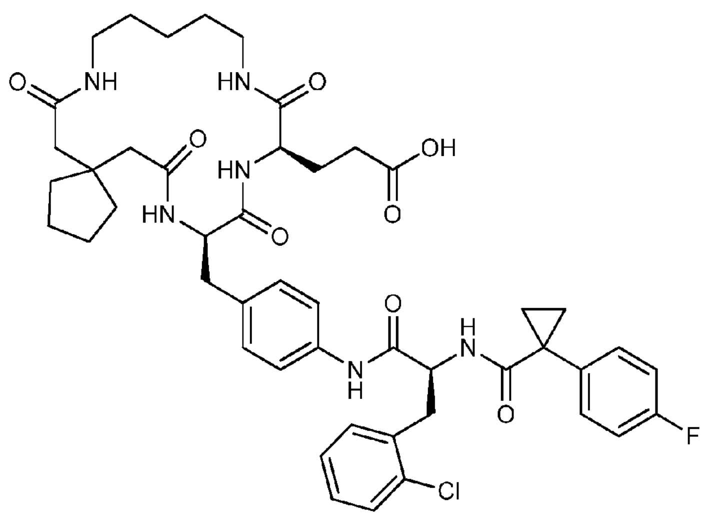
Compound No.	Structure
471	
472	

FIG. 12-170

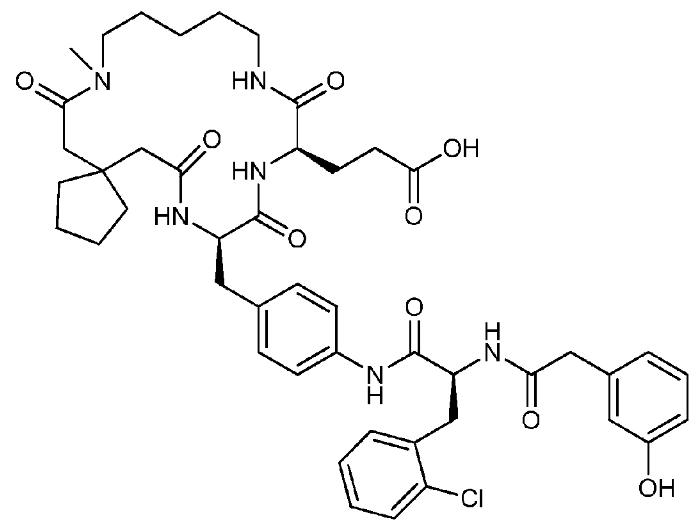
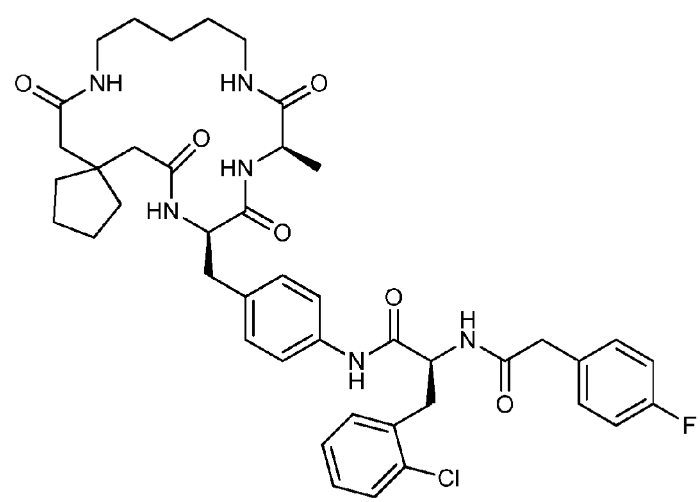
Compound No.	Structure
473	
474	

FIG. 12-171

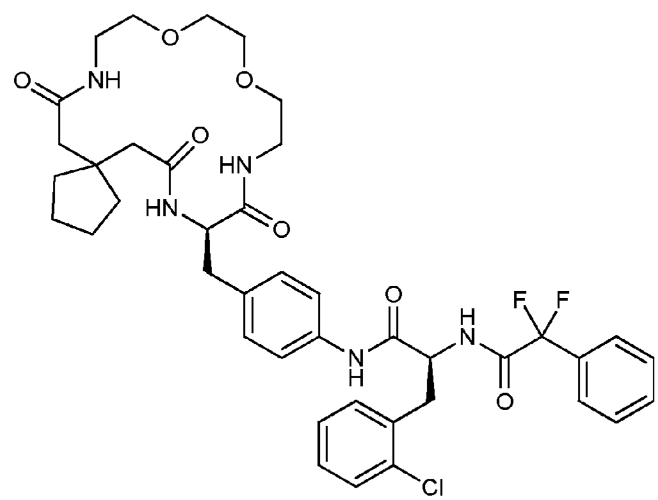
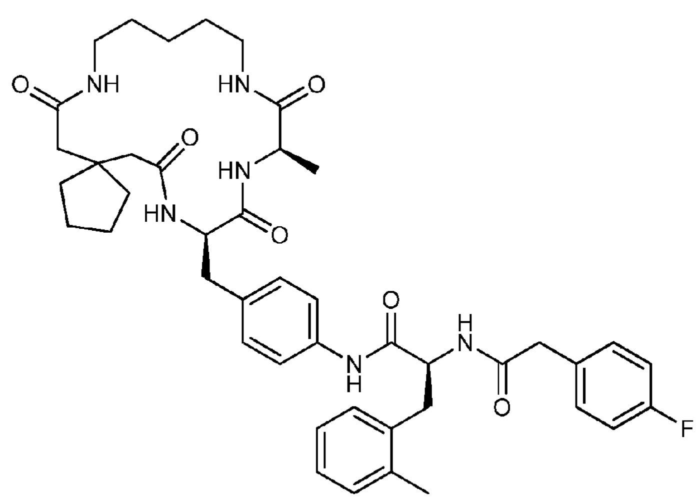
Compound No.	Structure
475	
476	

FIG. 12-172

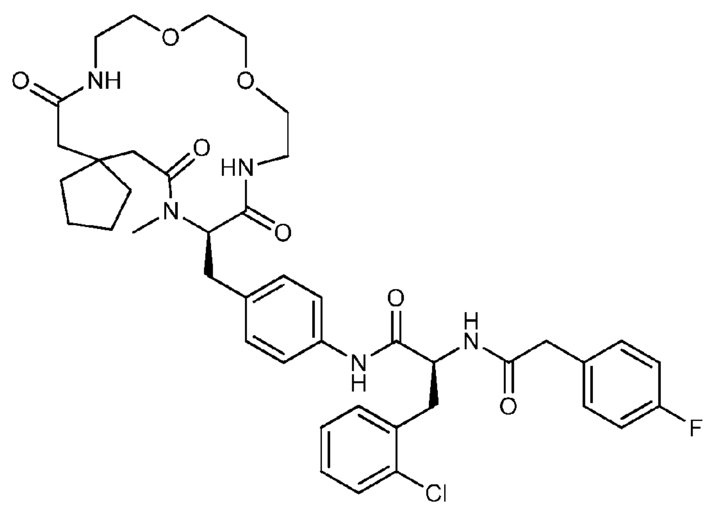
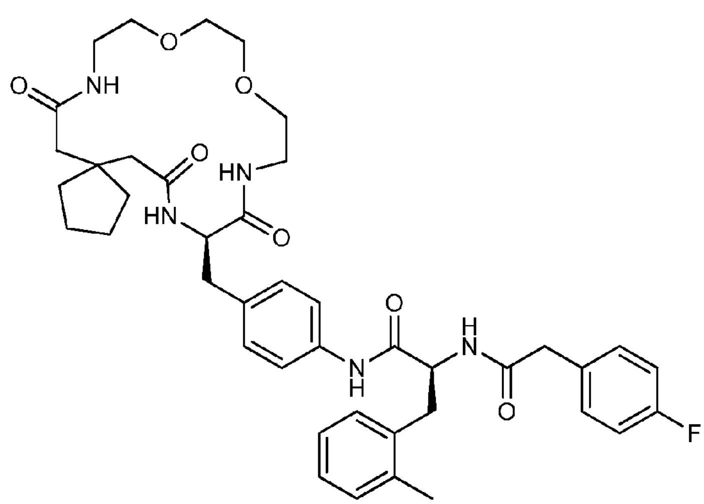
Compound No.	Structure
477	
478	

FIG. 12-173

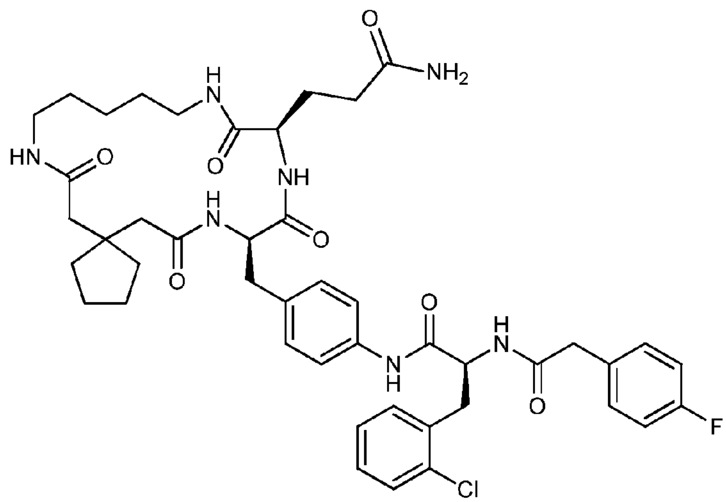
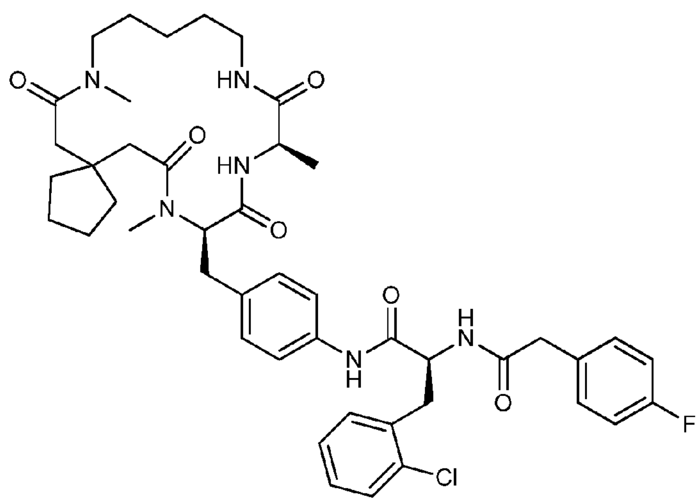
Compound No.	Structure
479	
480	

FIG. 12-174

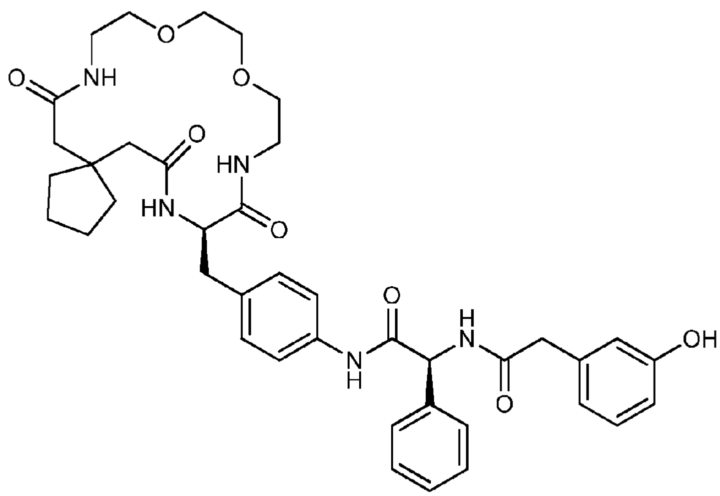
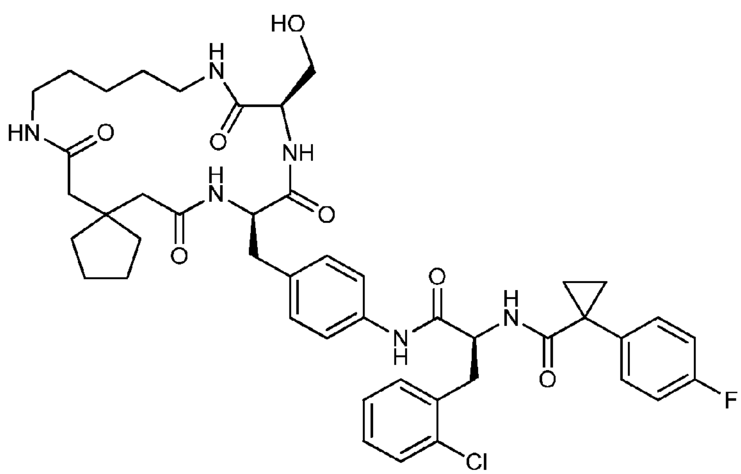
Compound No.	Structure
481	
482	

FIG. 12-175

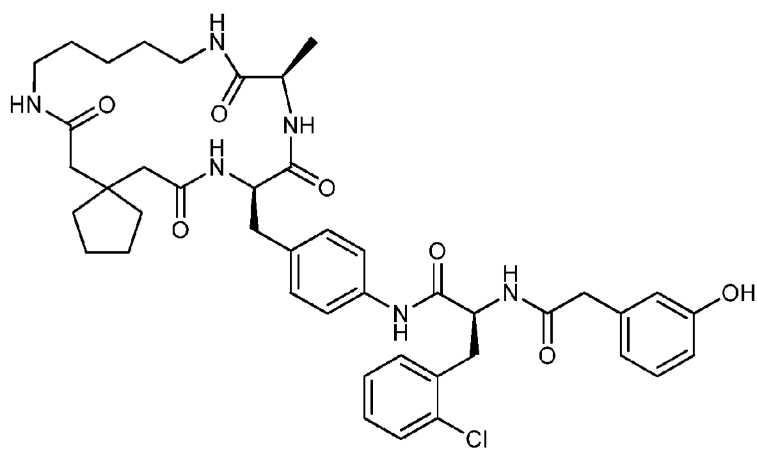
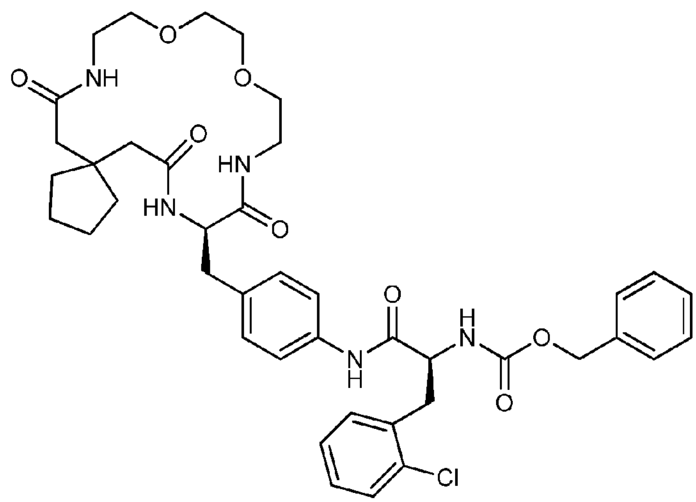
Compound No.	Structure
483	
484	

FIG. 12-176

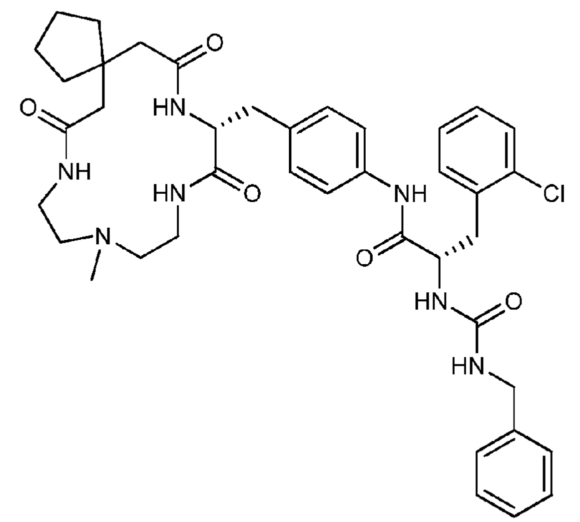
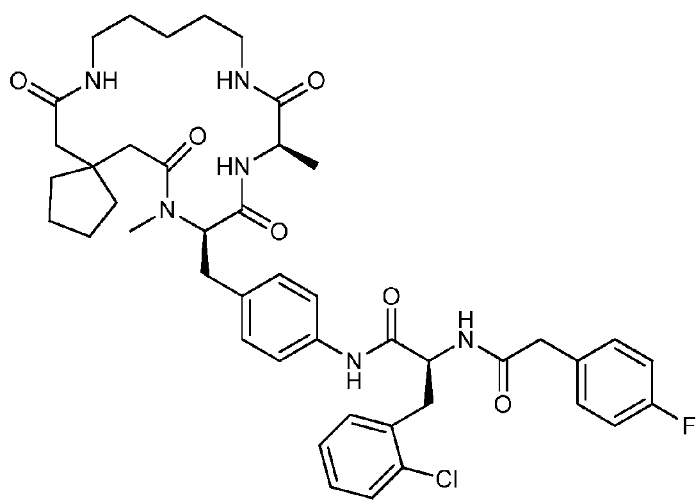
Compound No.	Structure
485	
486	

FIG. 12-177

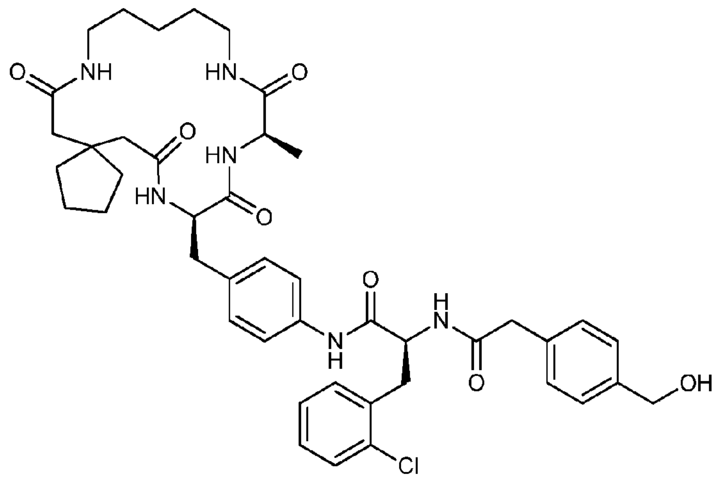
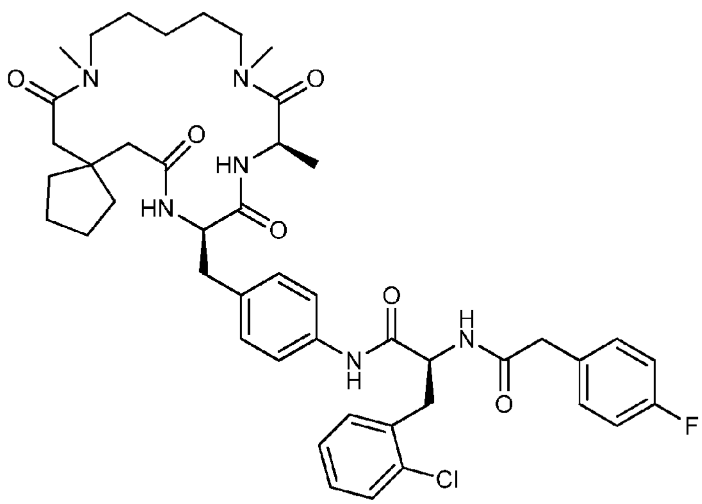
Compound No.	Structure
487	
488	

FIG. 12-178

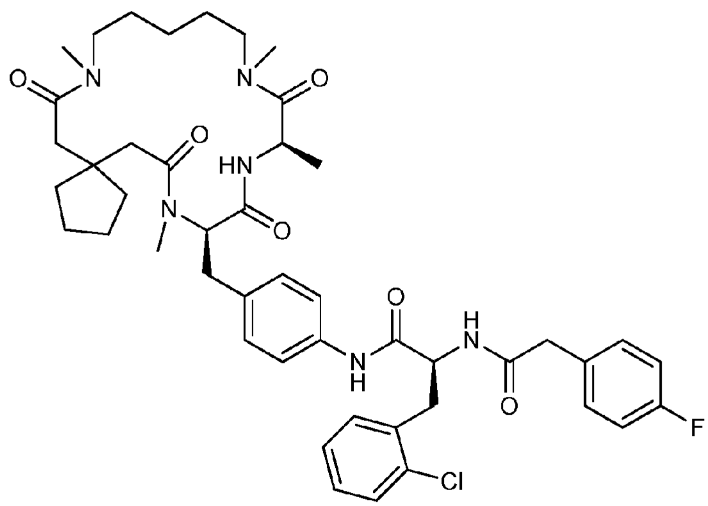
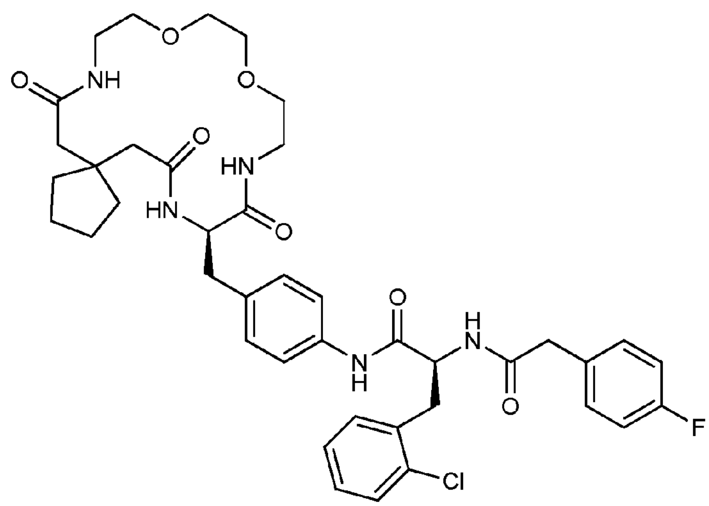
Compound No.	Structure
489	
490	

FIG. 12-179

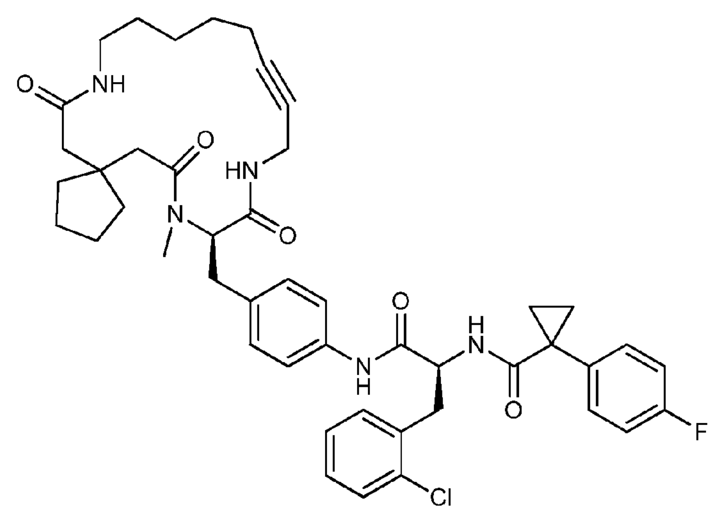
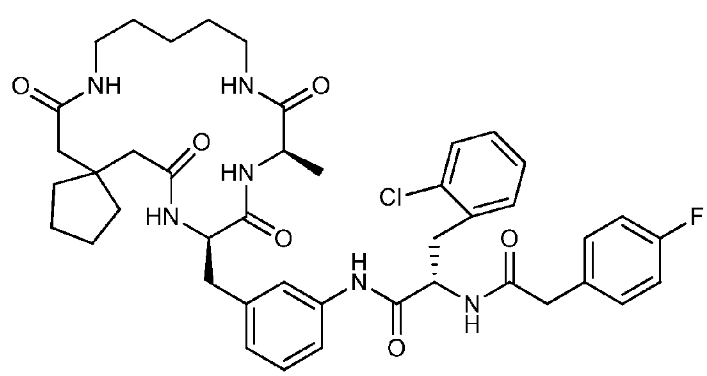
Compound No.	Structure
491	
492	

FIG. 12-180

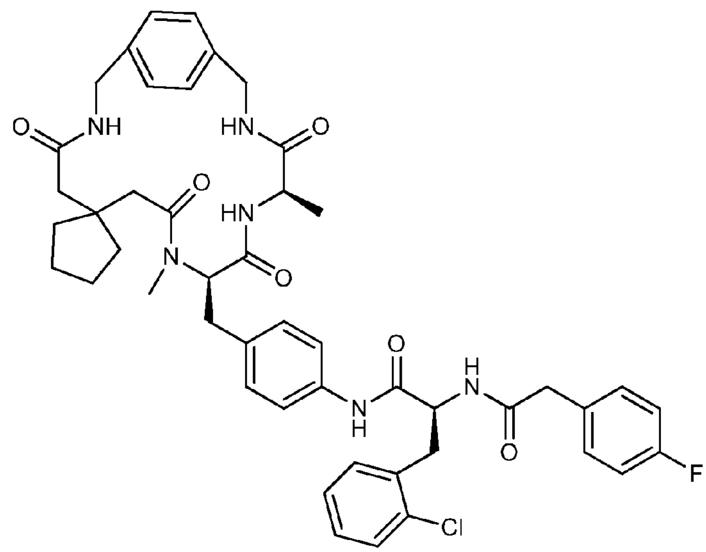
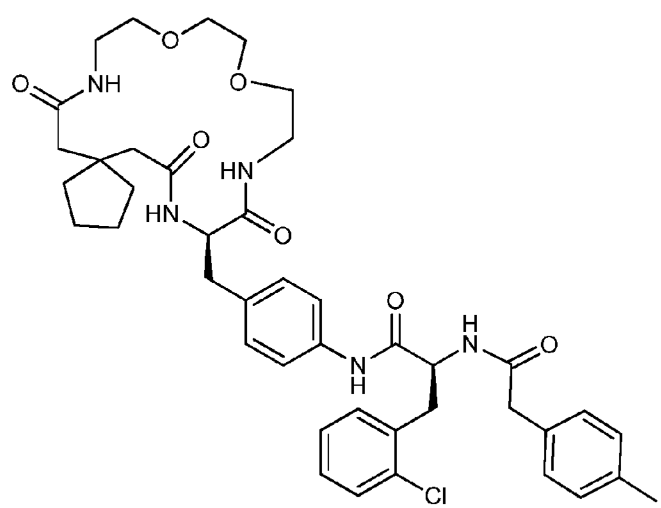
Compound No.	Structure
493	
494	

FIG. 12-181

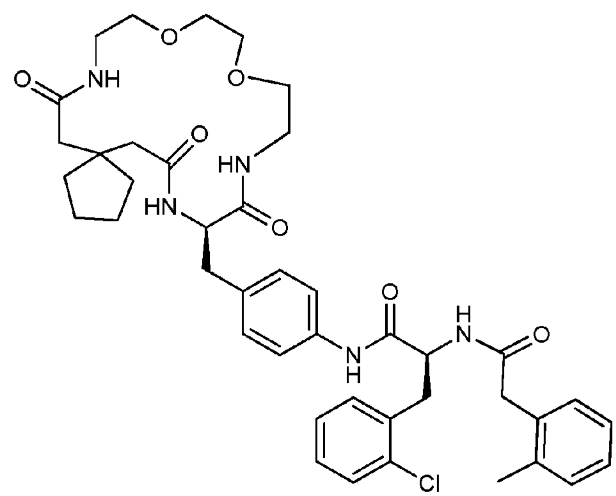
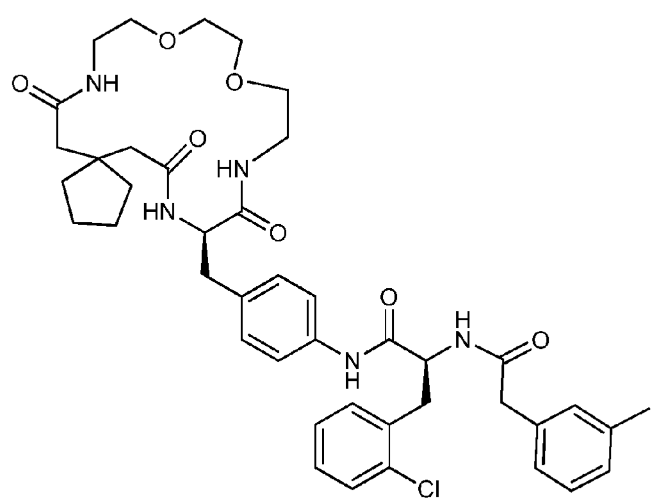
Compound No.	Structure
495	
496	

FIG. 12-182

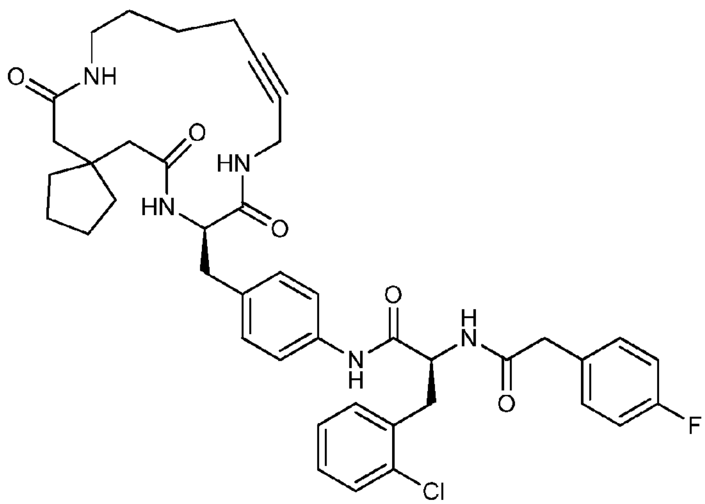
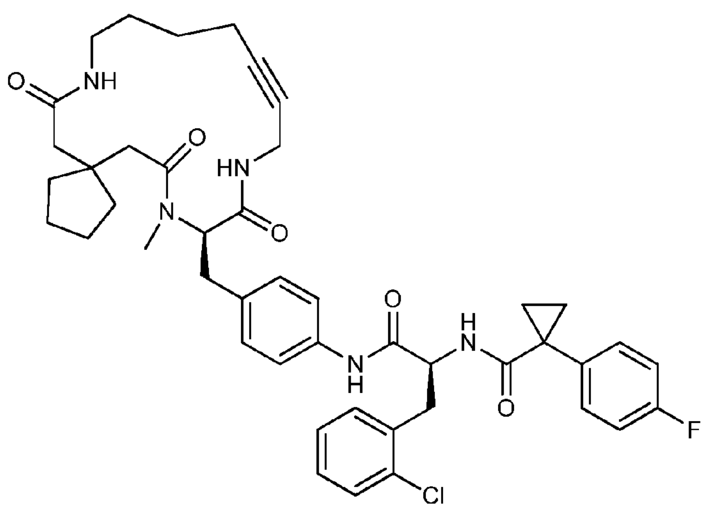
Compound No.	Structure
497	
498	

FIG. 12-183

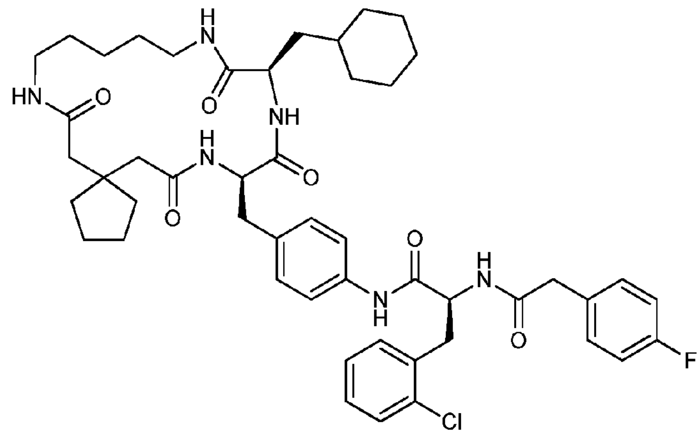
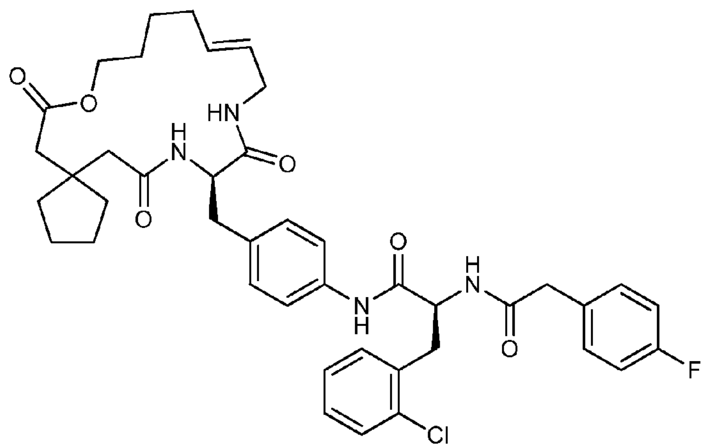
Compound No.	Structure
499	
500	

FIG. 12-184

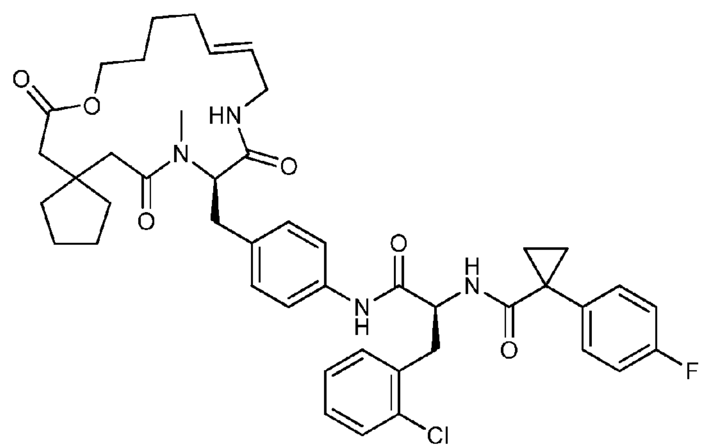
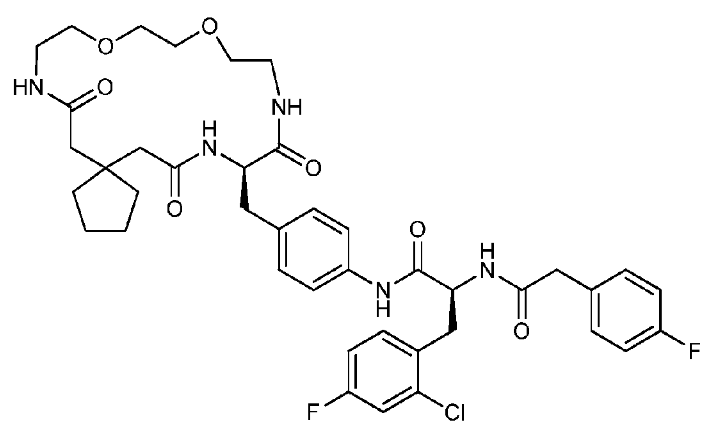
Compound No.	Structure
501	
502	

FIG. 12-185

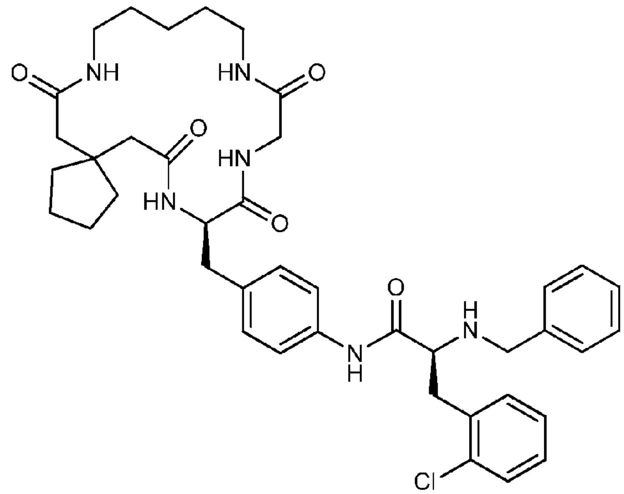
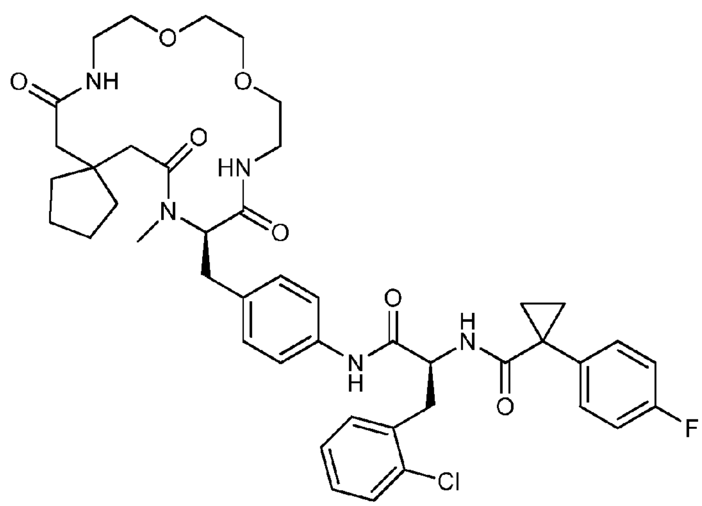
Compound No.	Structure
503	
504	

FIG. 12-186

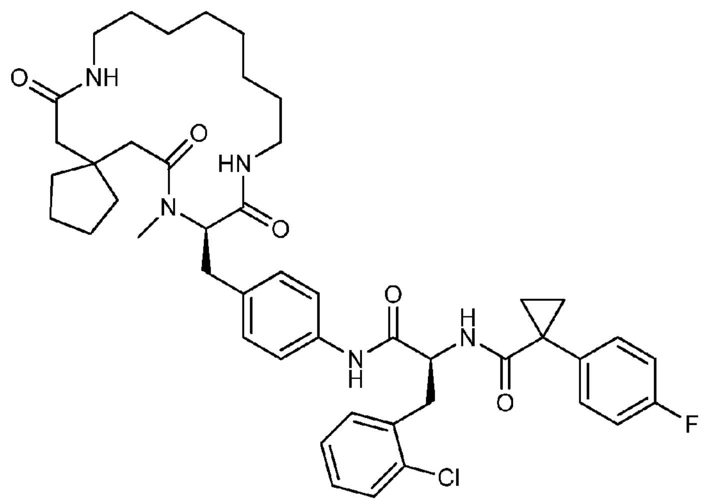
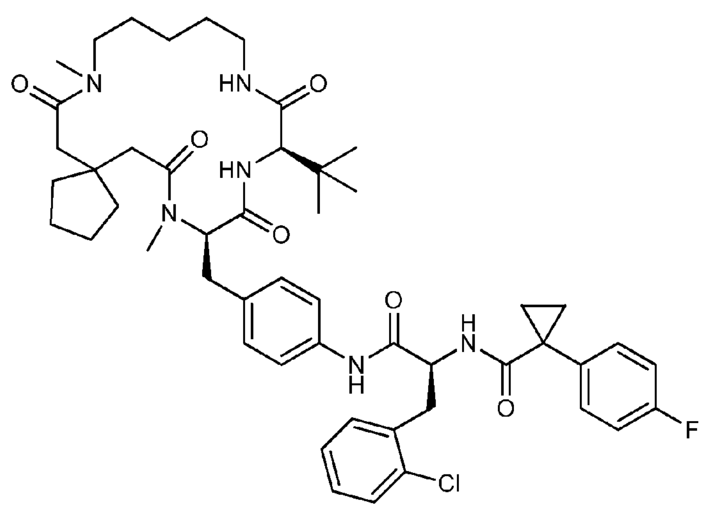
Compound No.	Structure
505	
506	

FIG. 12-187

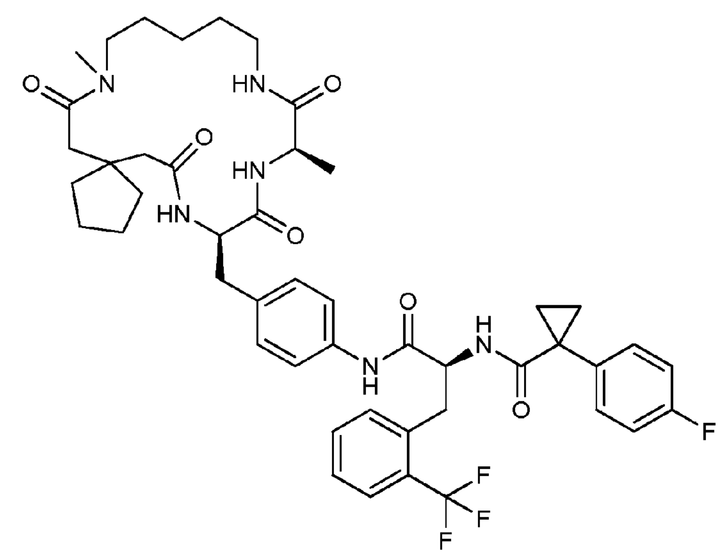
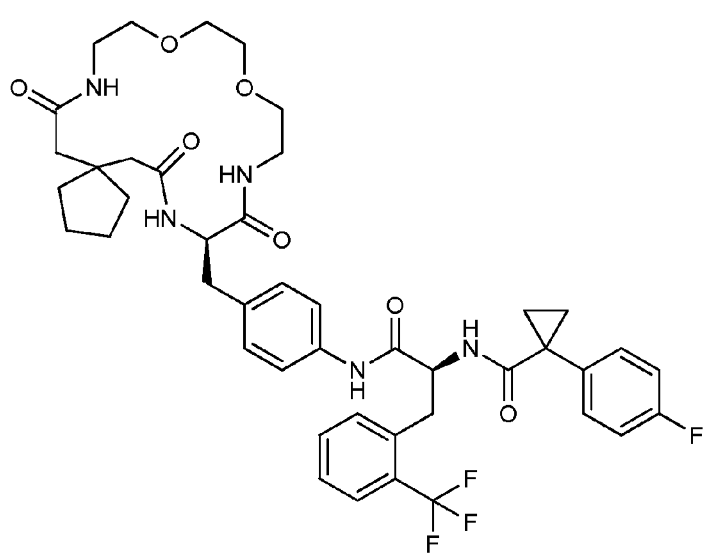
Compound No.	Structure
507	
508	

FIG. 12-188

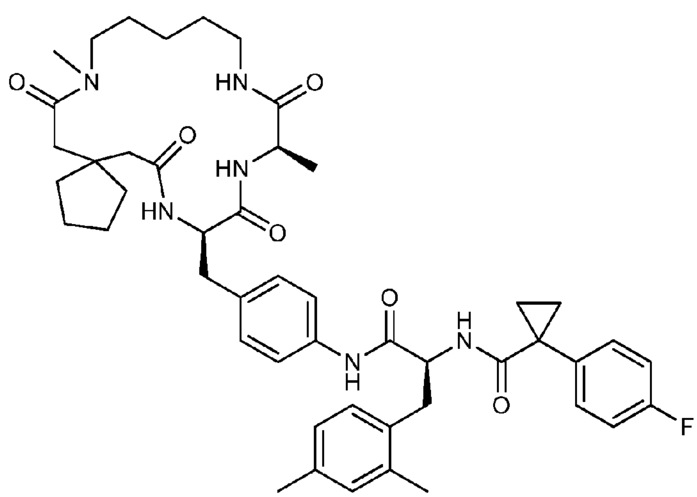
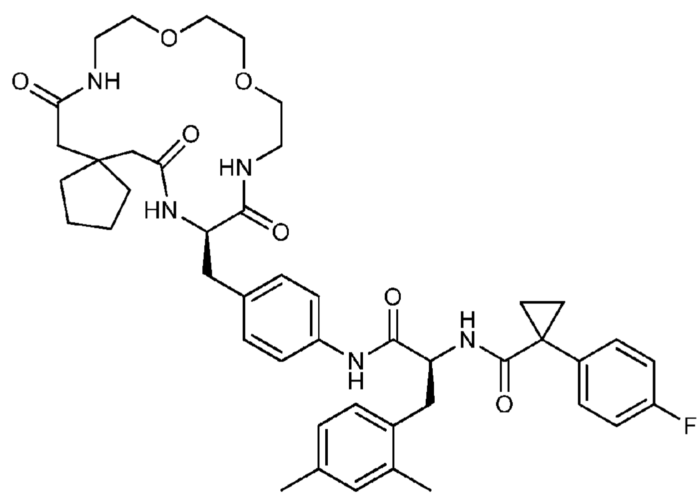
Compound No.	Structure
509	
510	

FIG. 12-189

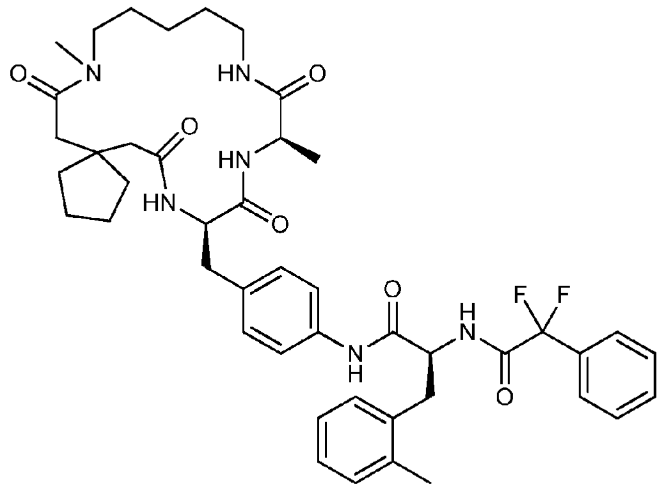
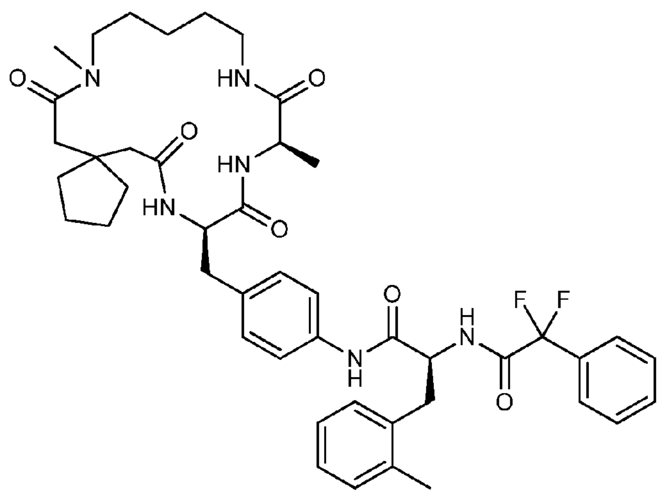
Compound No.	Structure
511	
512	

FIG. 12-190

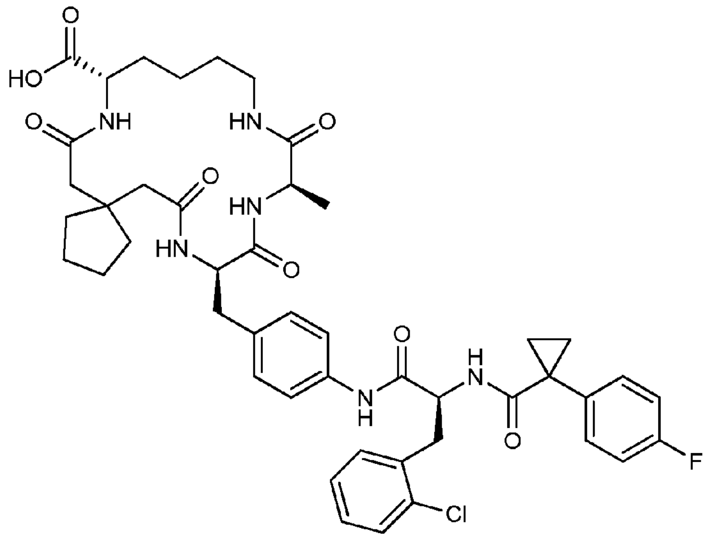
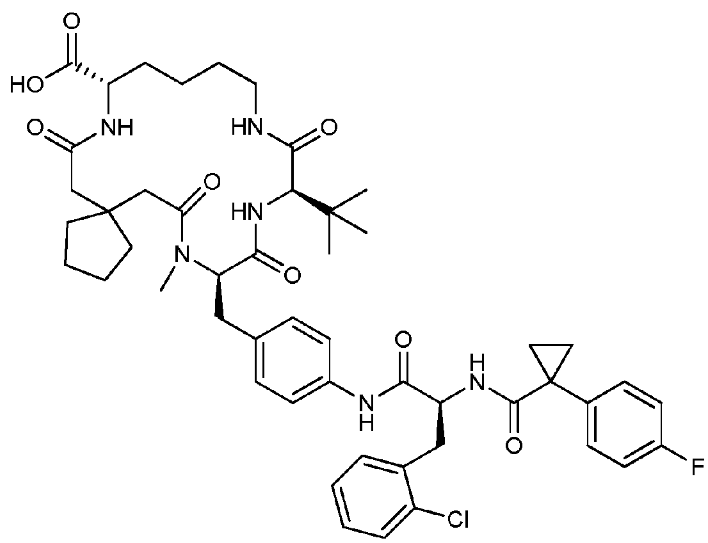
Compound No.	Structure
513	
514	

FIG. 12-191

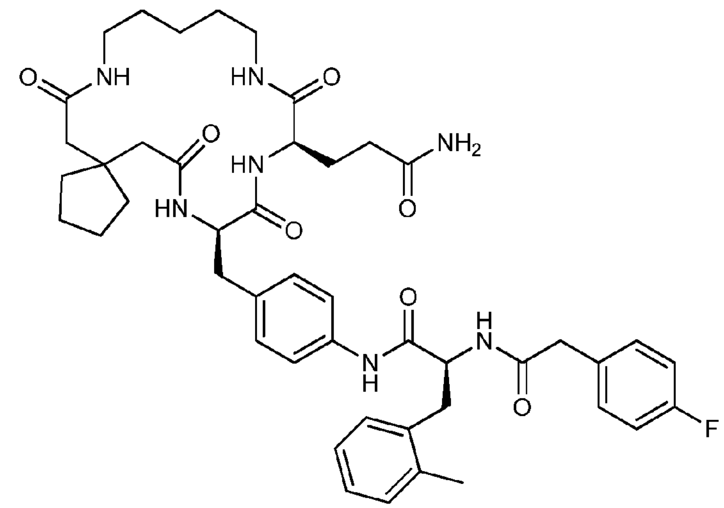
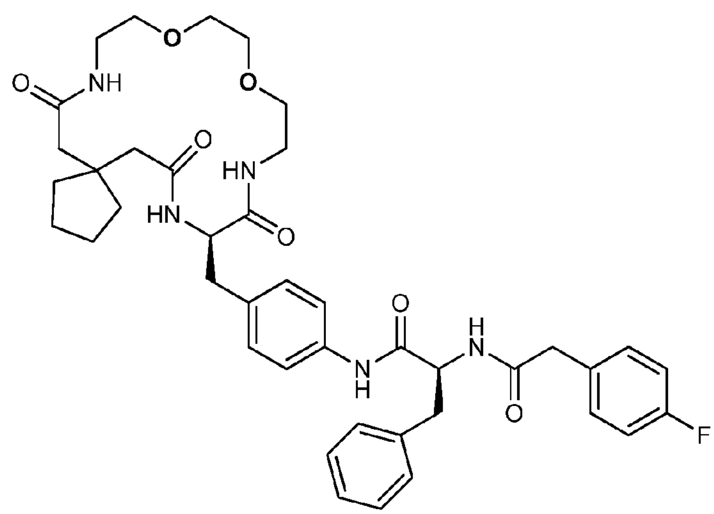
Compound No.	Structure
515	
516	

FIG. 12-192

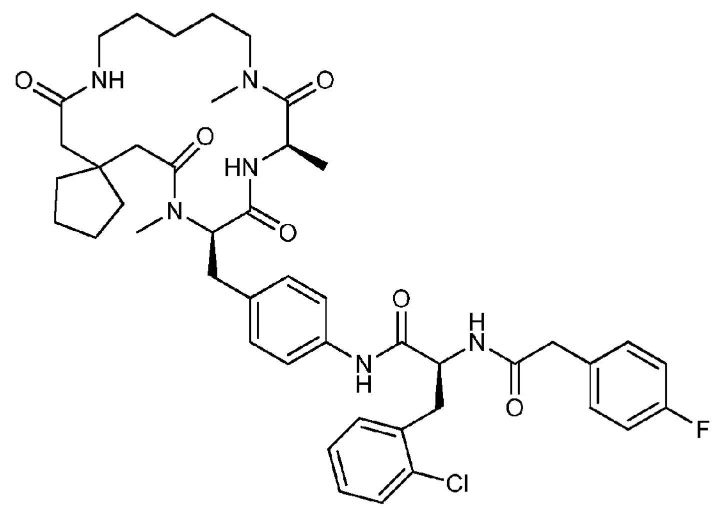
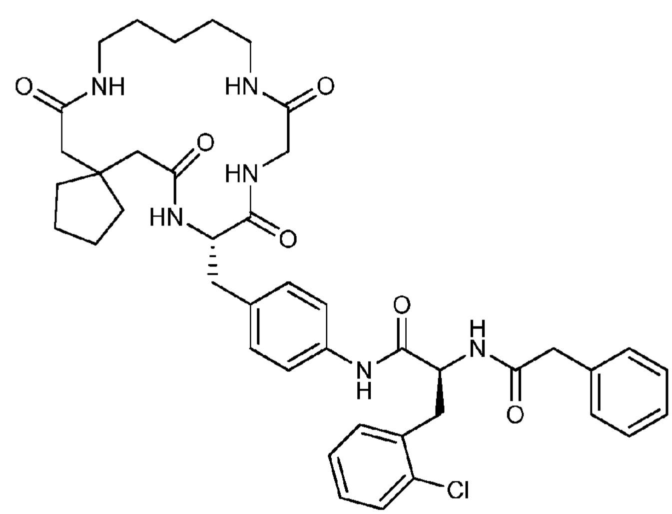
Compound No.	Structure
518	
519	

FIG. 12-193

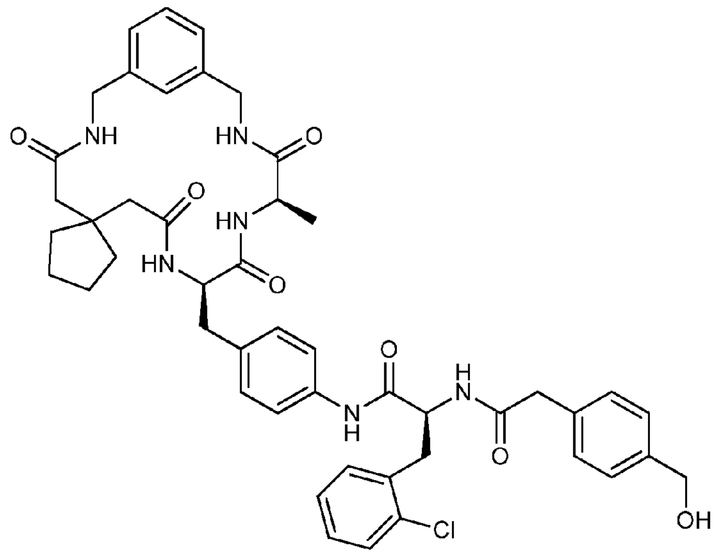
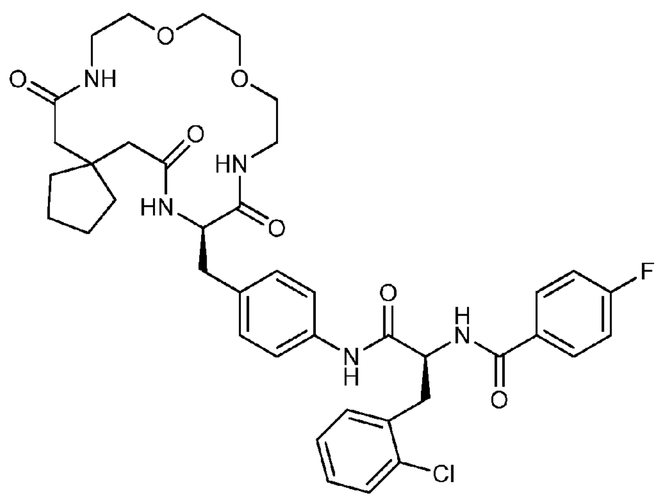
Compound No.	Structure
520	
521	

FIG. 12-194

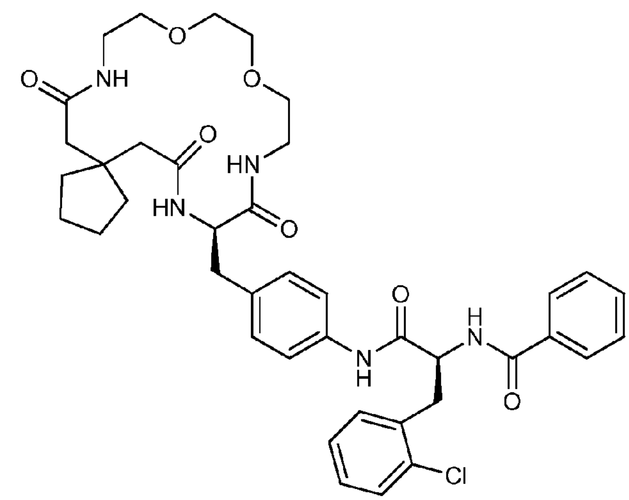
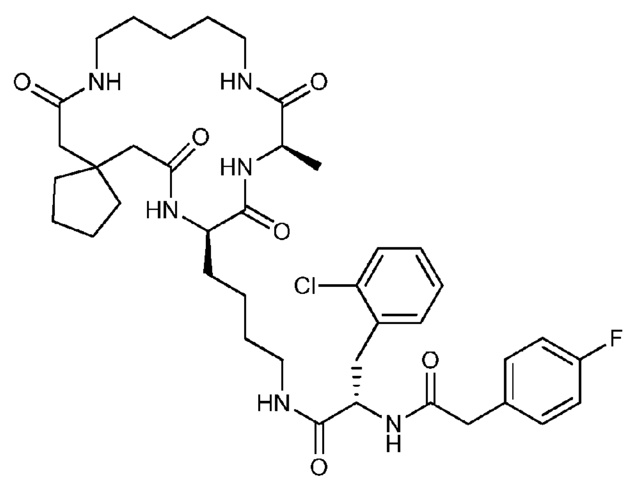
Compound No.	Structure
522	
523	

FIG. 12-195

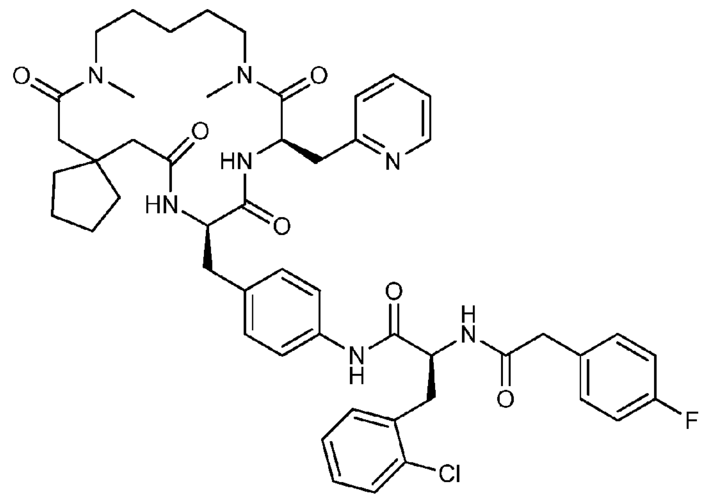
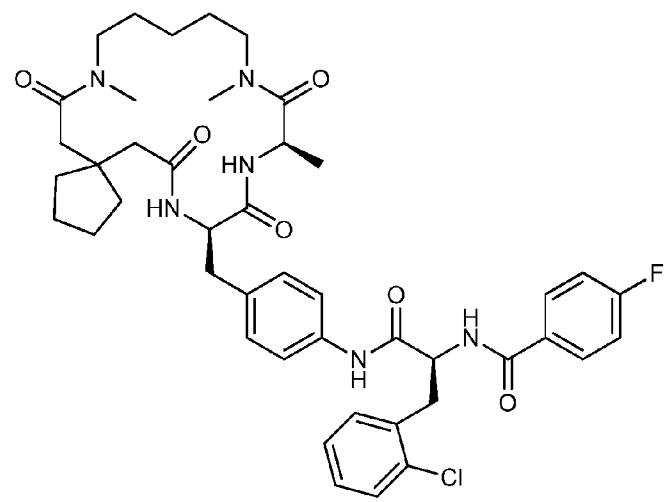
Compound No.	Structure
524	
525	

FIG. 12-196

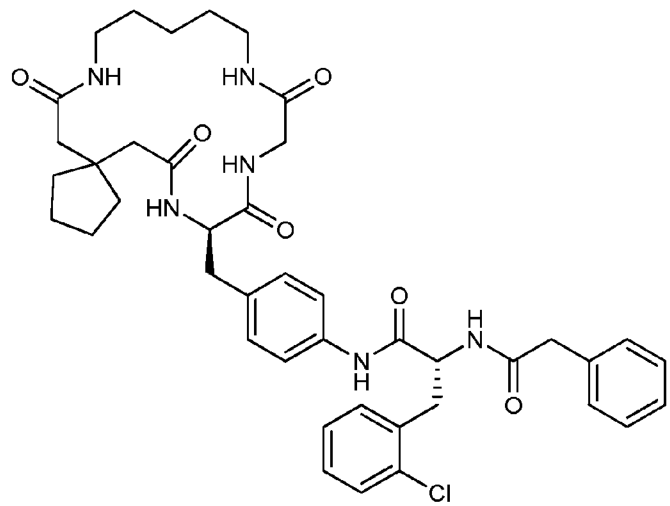
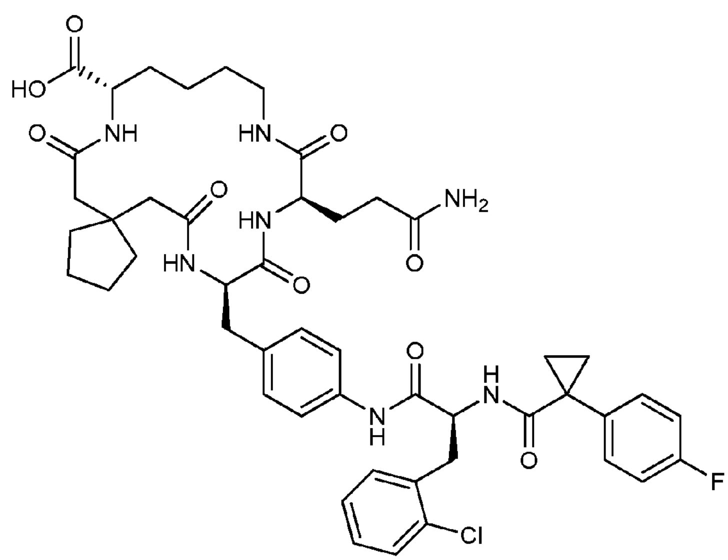
Compound No.	Structure
526	
527	

FIG. 12-197

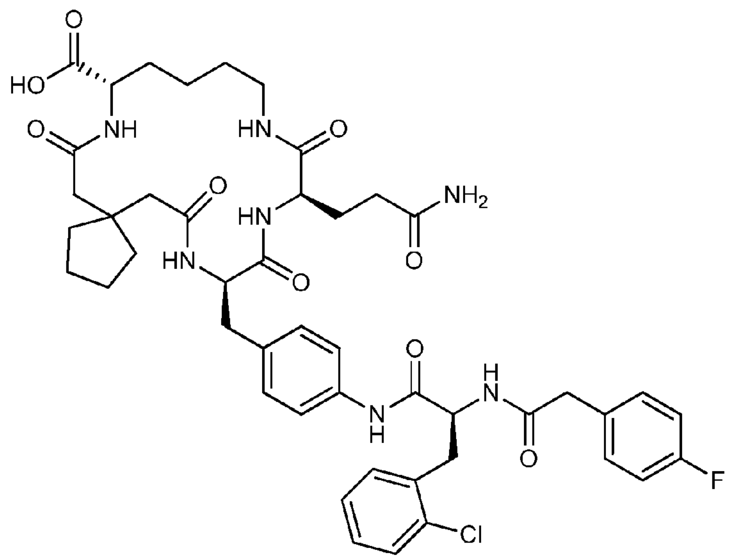
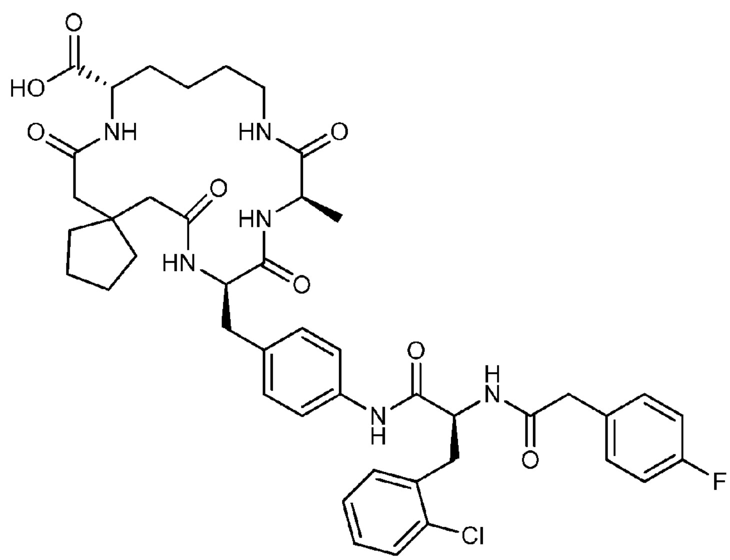
Compound No.	Structure
528	
529	

FIG. 12-198

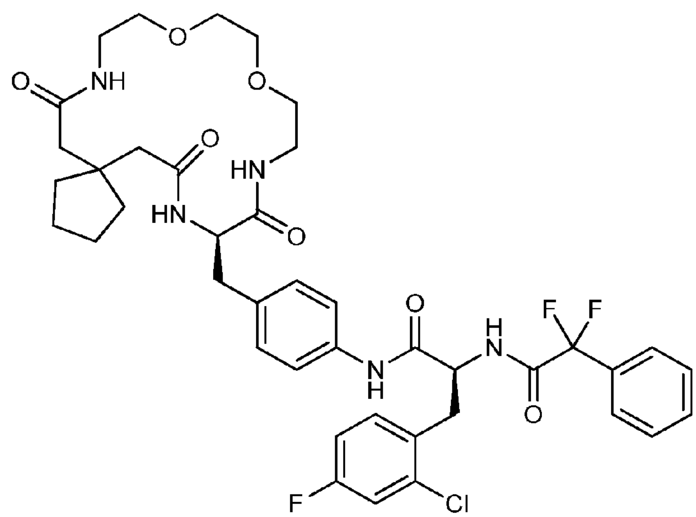
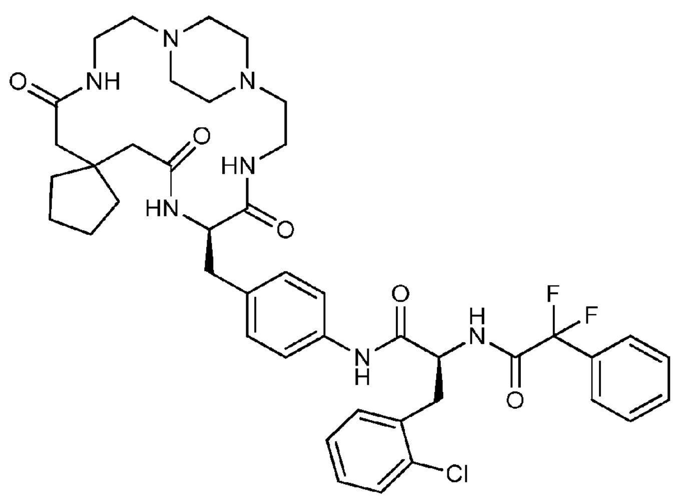
Compound No.	Structure
530	
531	

FIG. 12-199

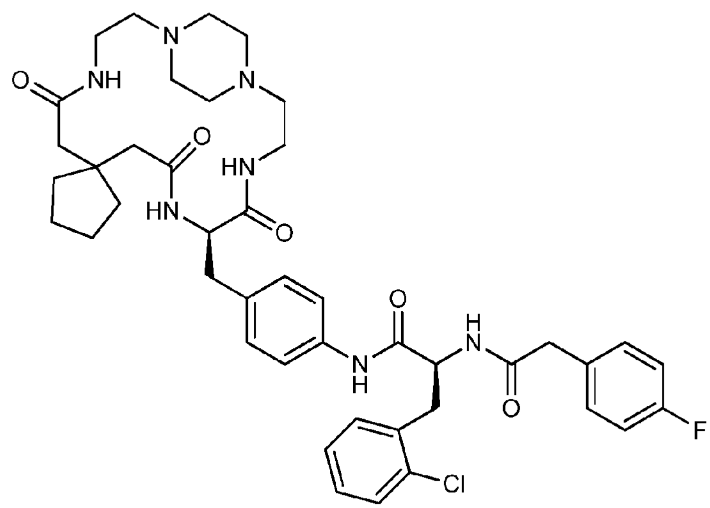
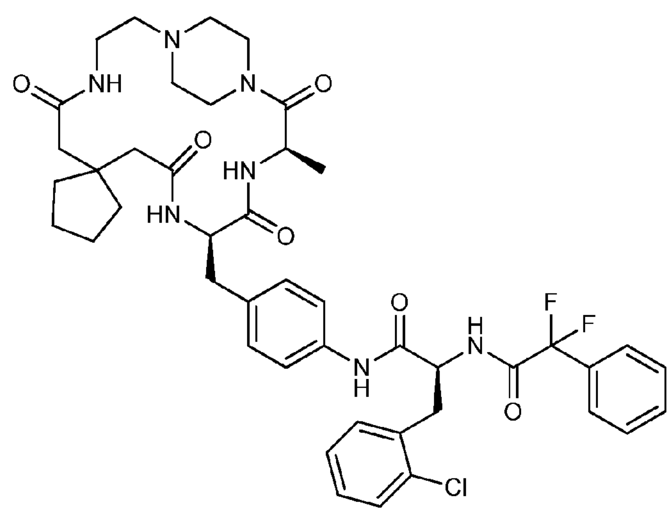
Compound No.	Structure
532	
533	

FIG. 12-200

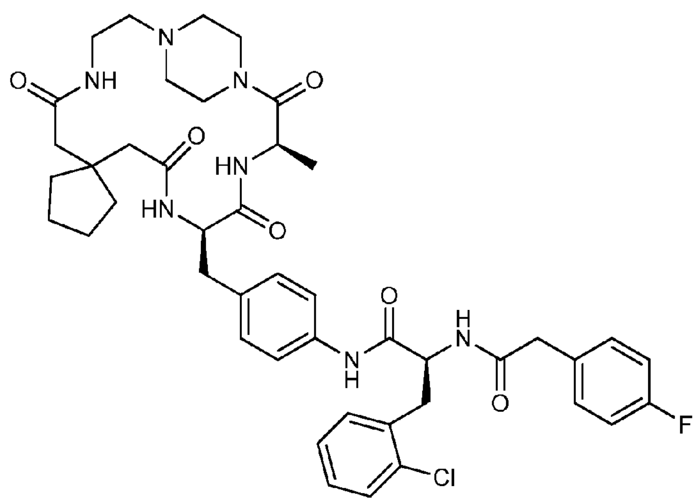
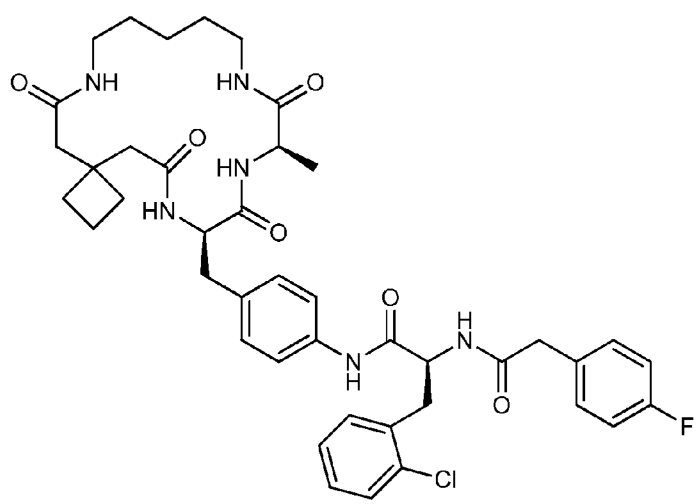
Compound No.	Structure
534	
535	

FIG. 12-201

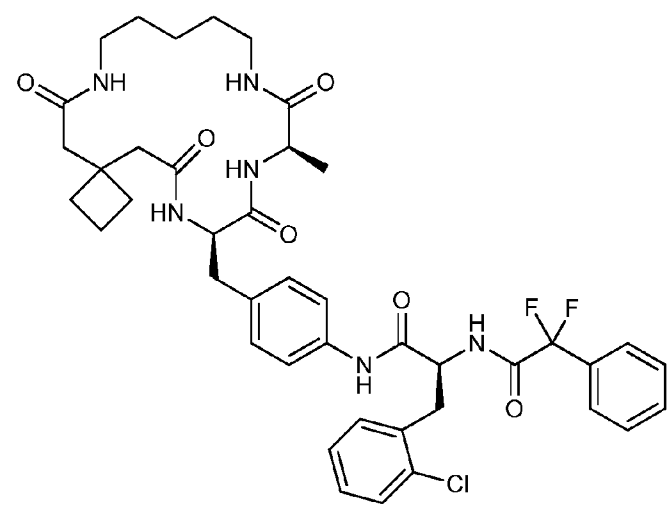
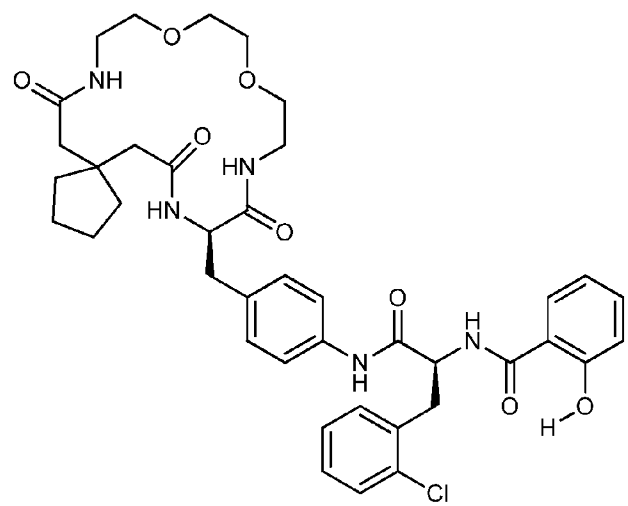
Compound No.	Structure
536	
537	

FIG. 12-202

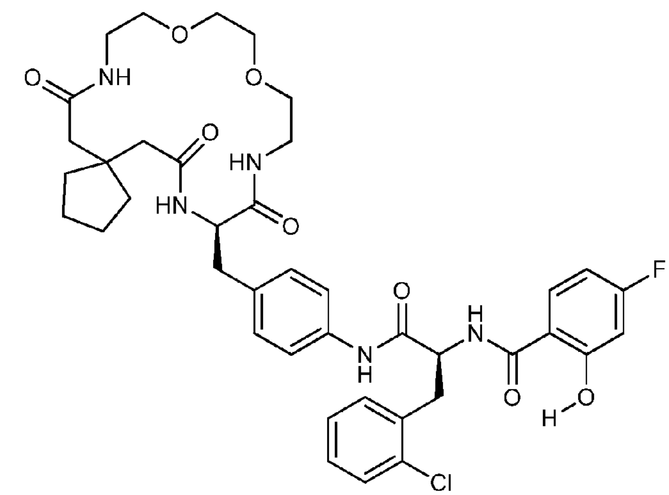
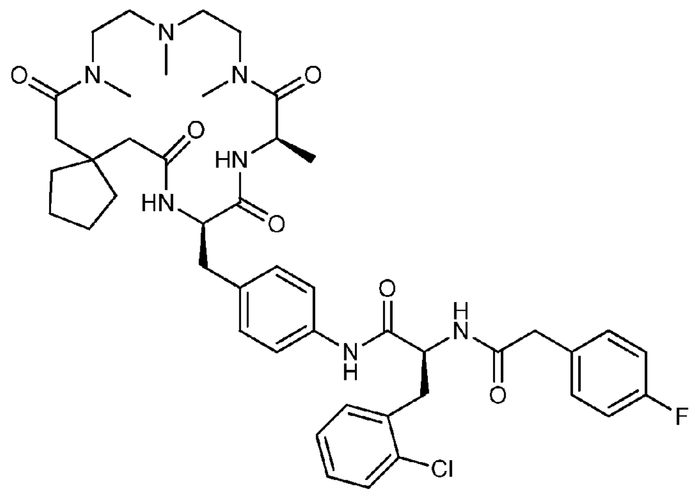
Compound No.	Structure
538	
539	

FIG. 12-203

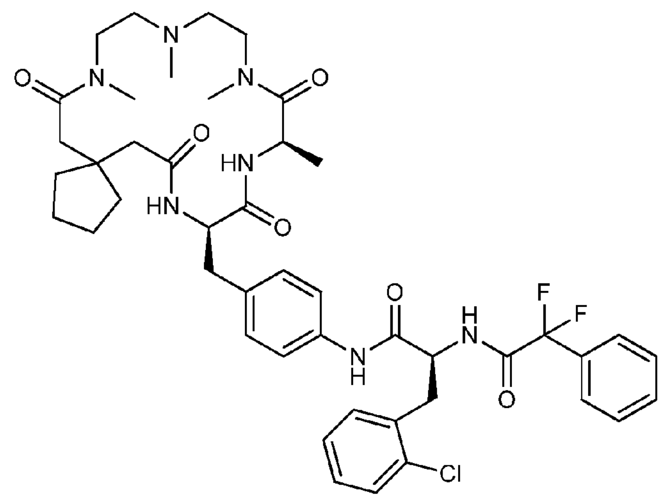
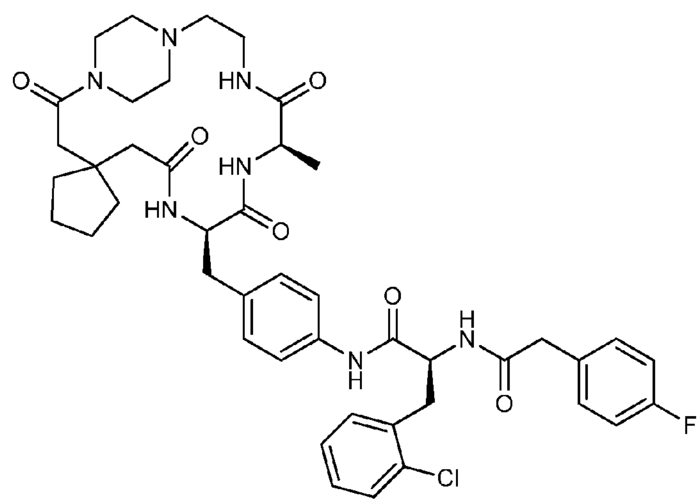
Compound No.	Structure
540	
541	

FIG. 12-204

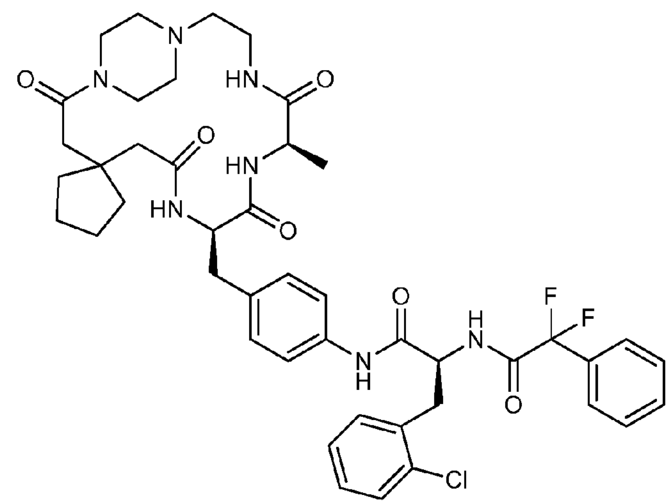
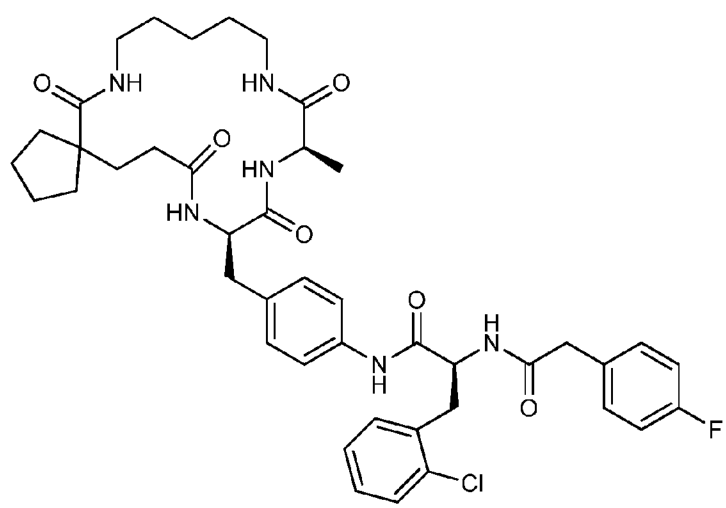
Compound No.	Structure
542	
543	

FIG. 12-205

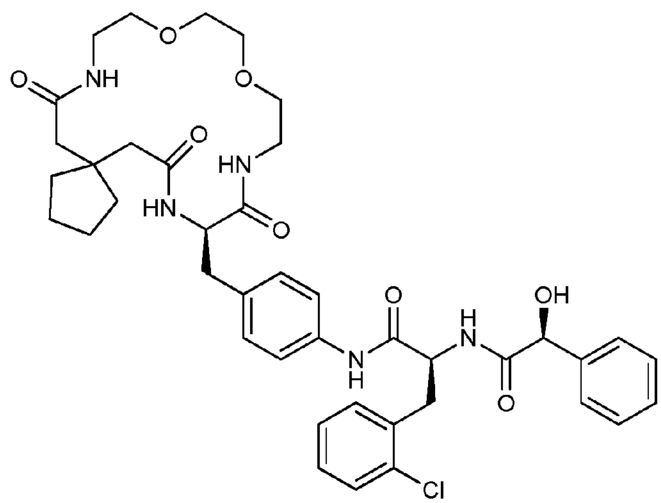
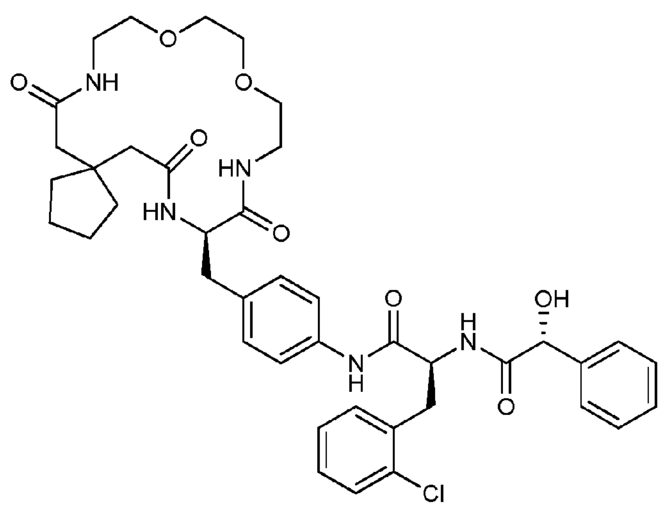
Compound No.	Structure
544	
545	

FIG. 12-206

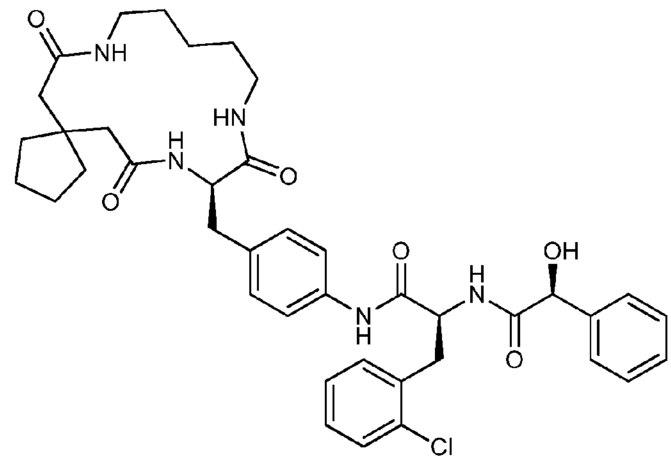
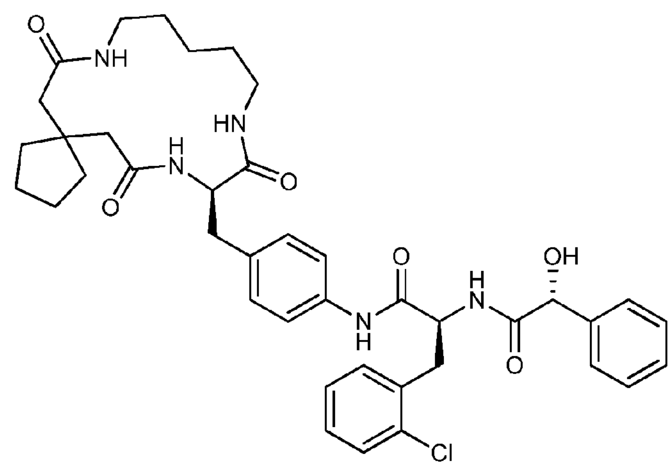
Compound No.	Structure
546	
547	

FIG. 12-207

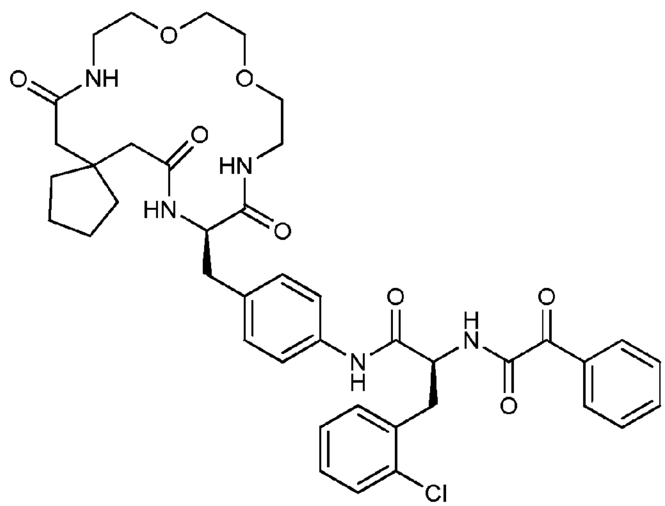
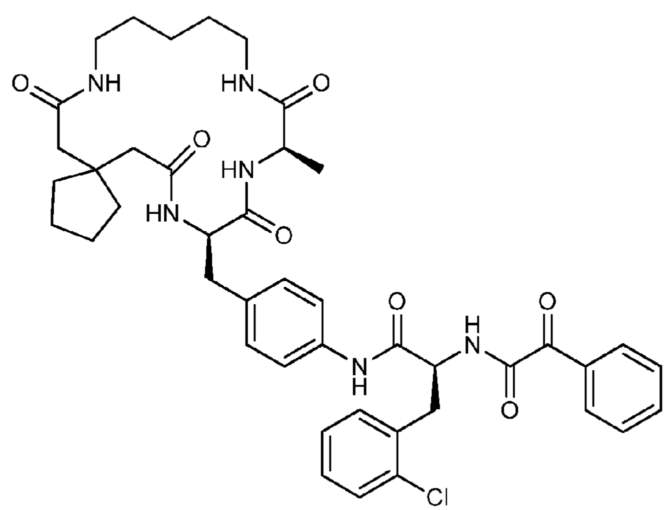
Compound No.	Structure
548	
549	

FIG. 12-208

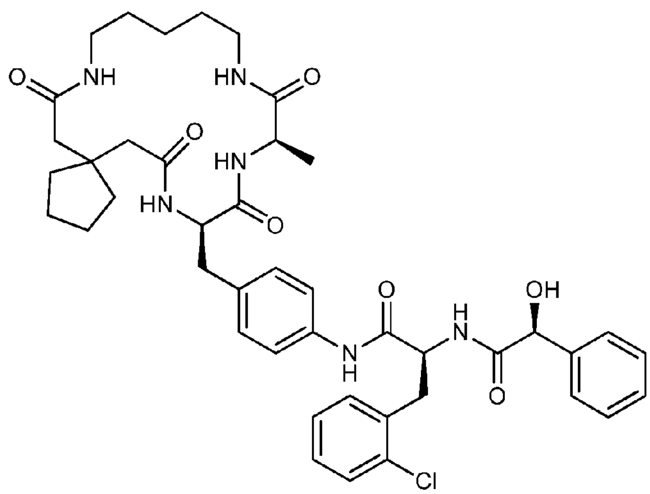
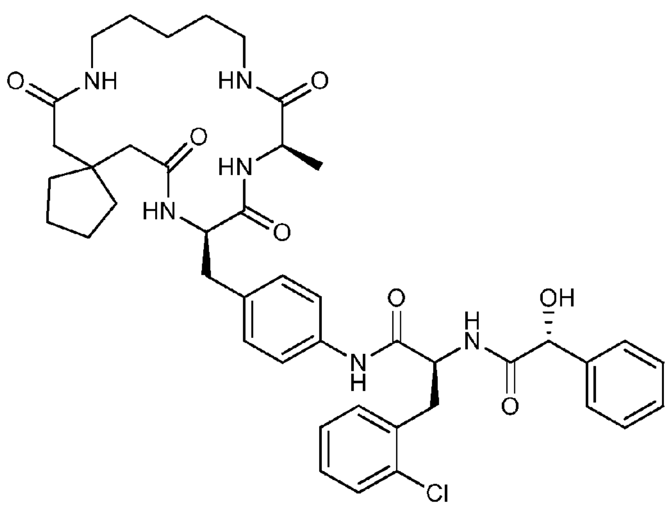
Compound No.	Structure
550	
551	

FIG. 12-209

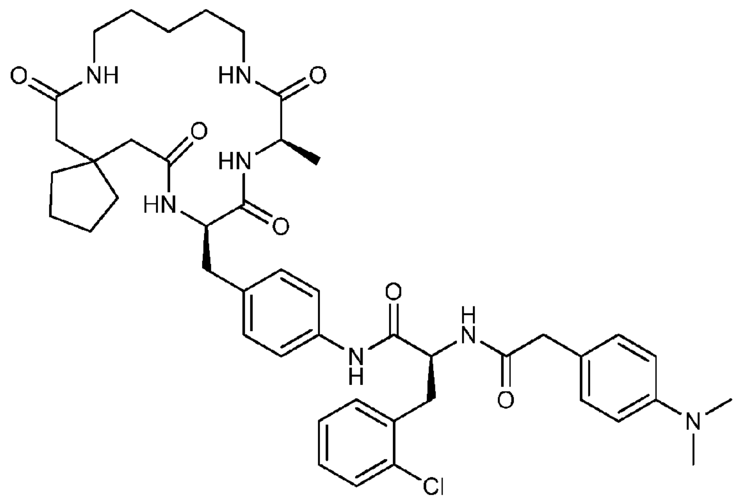
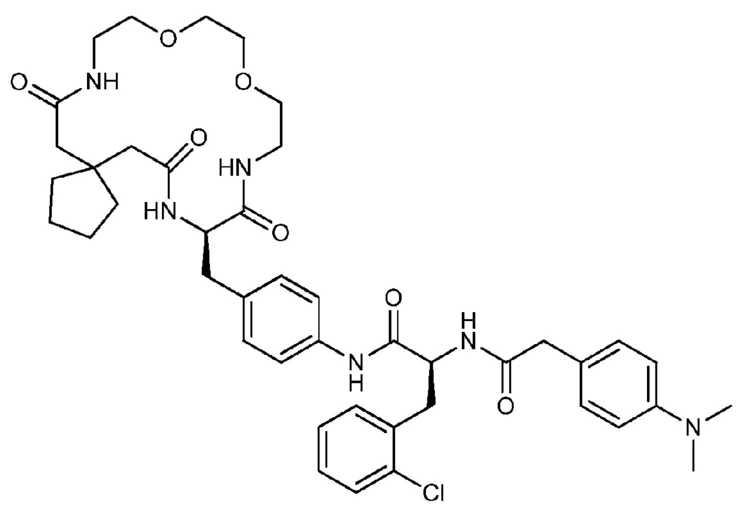
Compound No.	Structure
552	
553	

FIG. 12-210

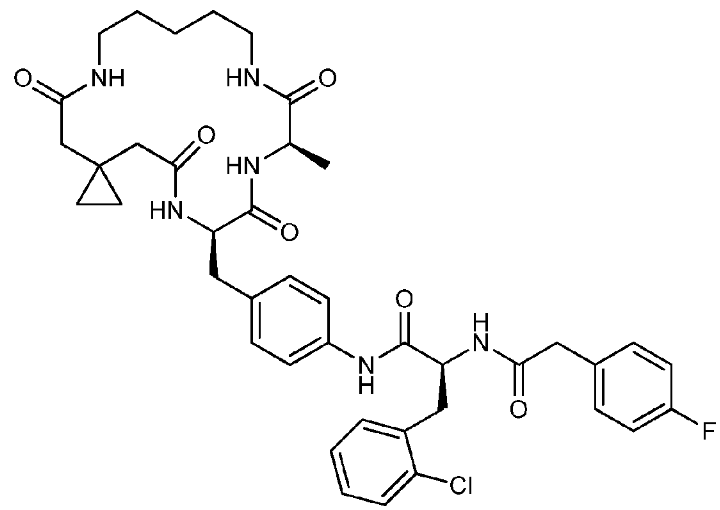
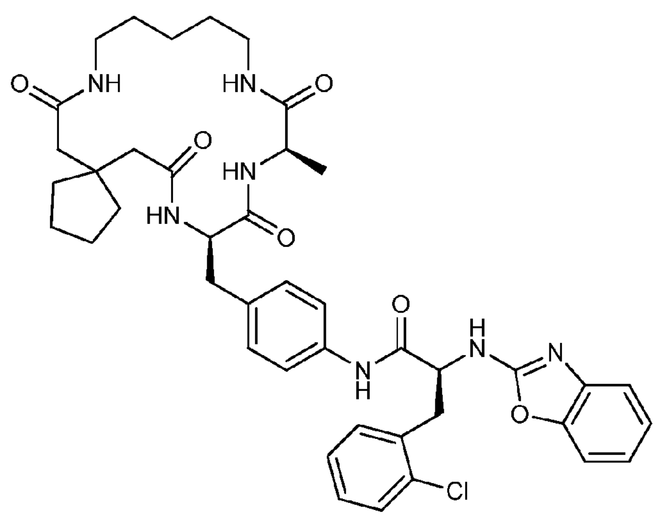
Compound No.	Structure
554	
555	

FIG. 12-211

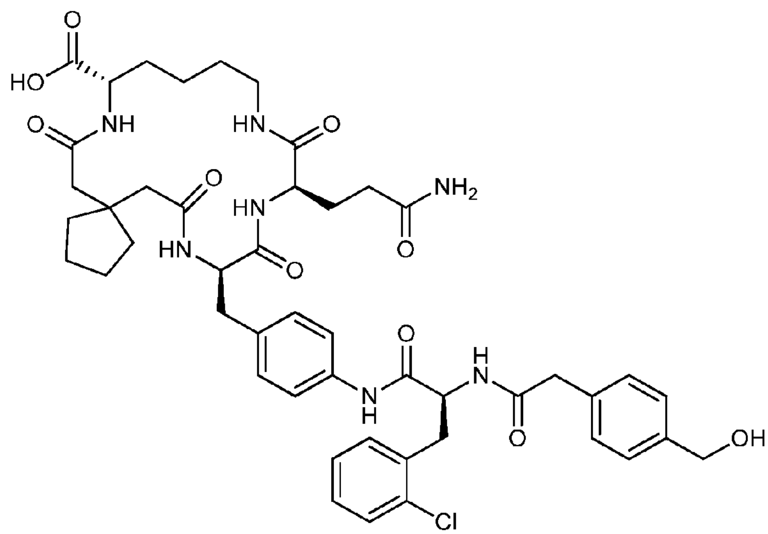
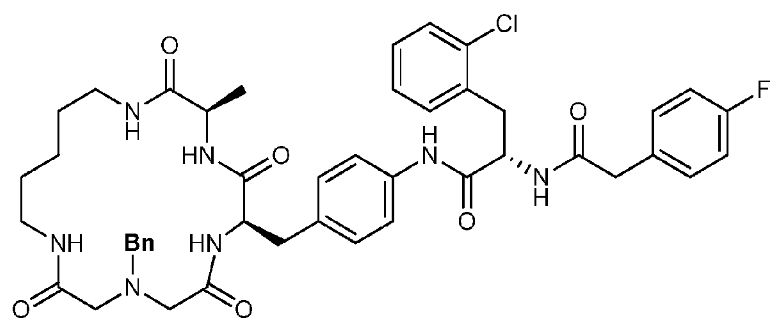
Compound No.	Structure
556	
557	

FIG. 12-212

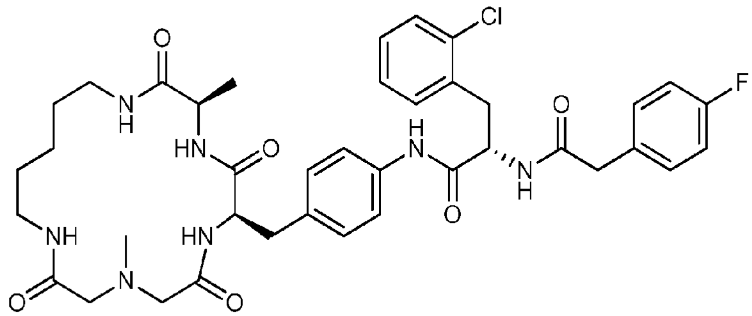
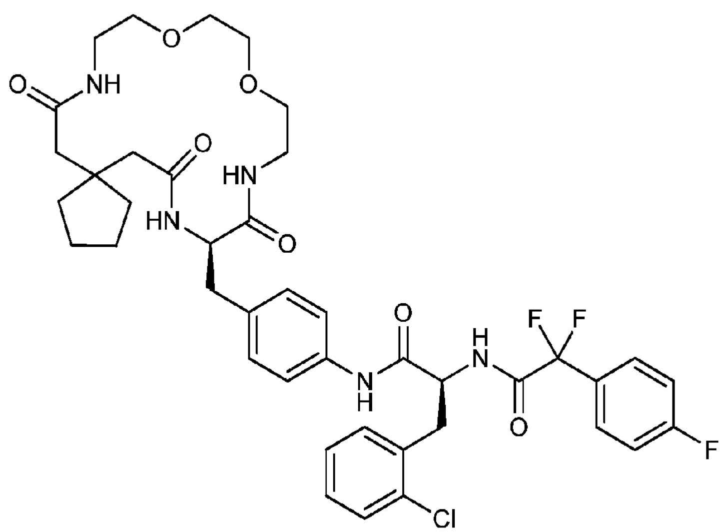
Compound No.	Structure
558	
559	

FIG. 12-213

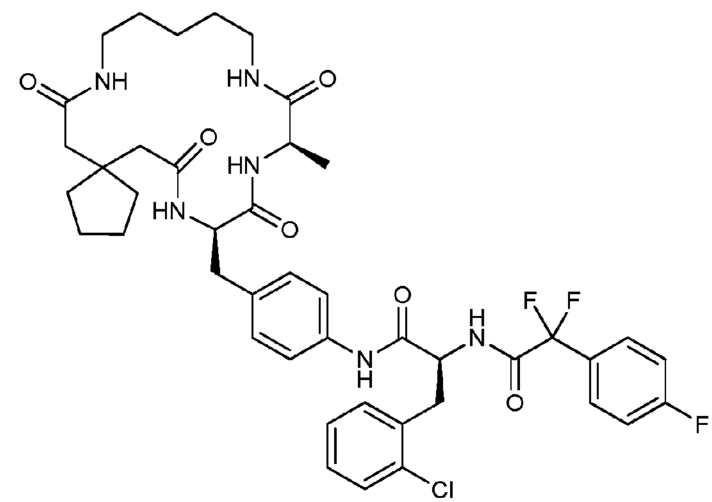
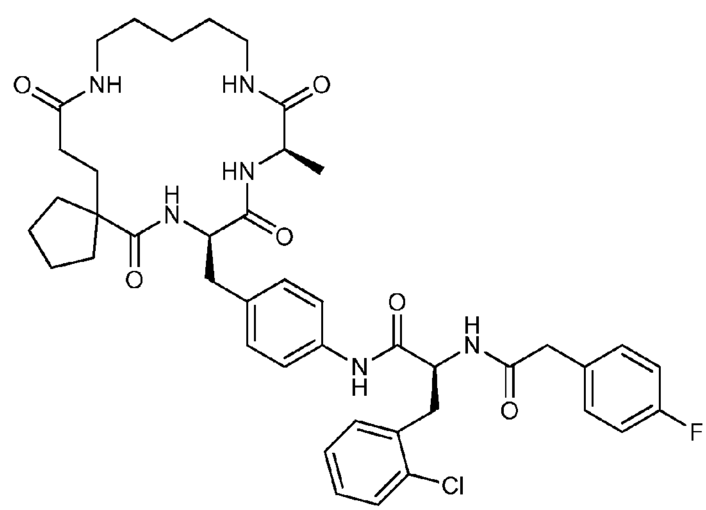
Compound No.	Structure
560	
561	

FIG. 12-214

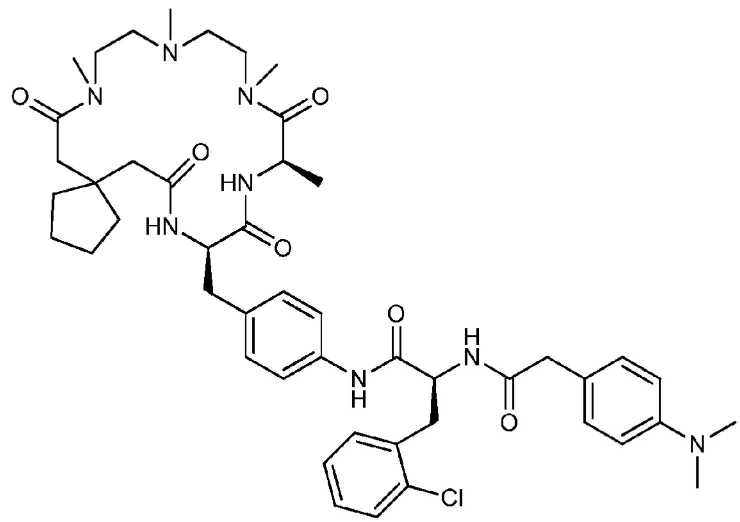
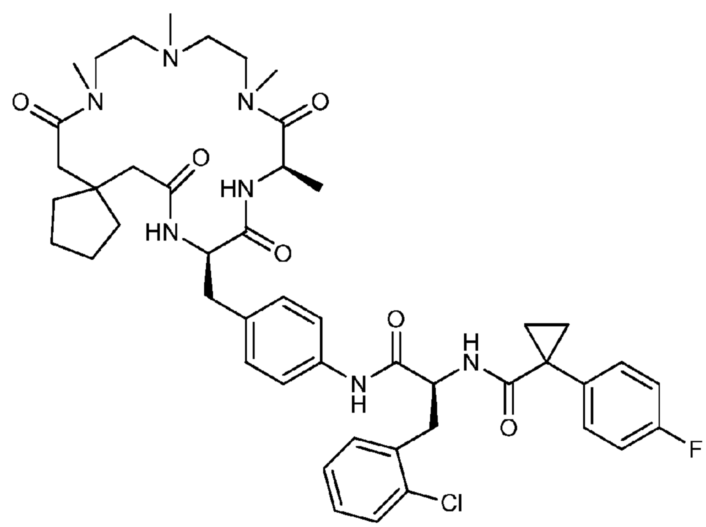
Compound No.	Structure
562	
563	

FIG. 12-215

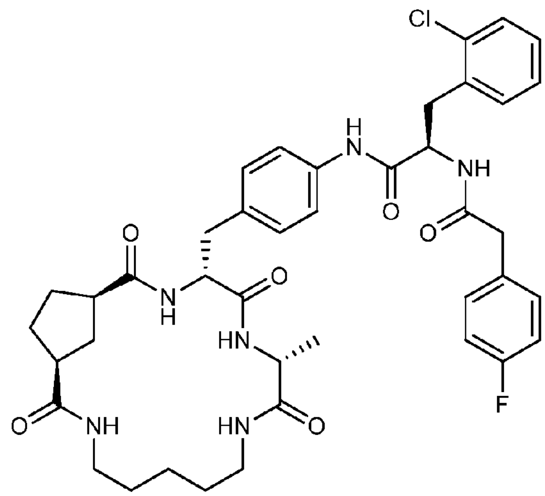
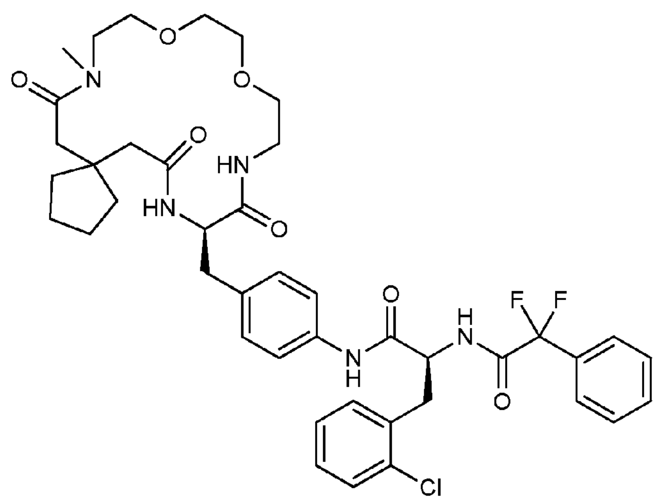
Compound No.	Structure
564	
565	

FIG. 12-216

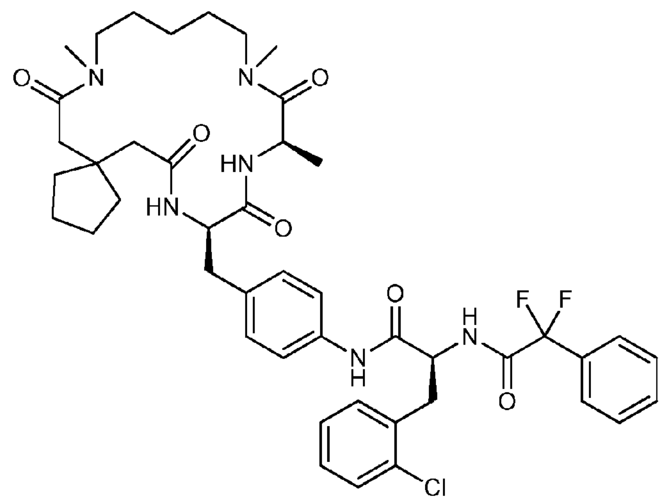
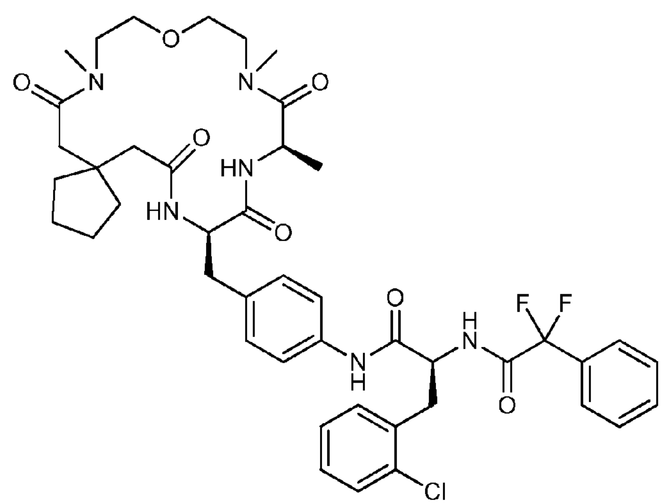
Compound No.	Structure
566	
567	

FIG. 12-217

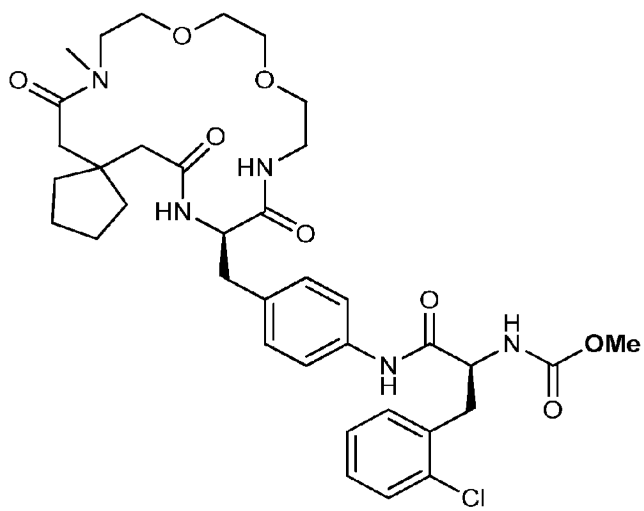
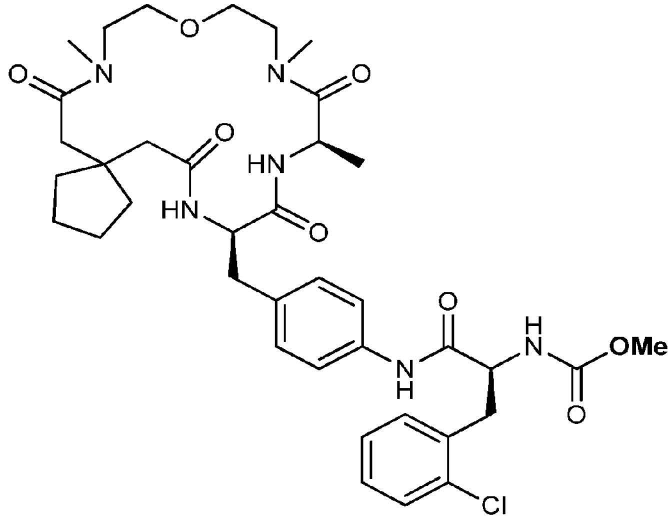
Compound No.	Structure
568	
569	

FIG. 12-218

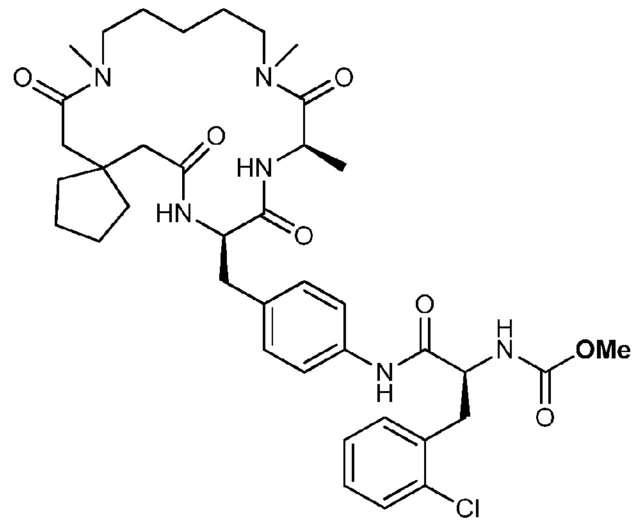
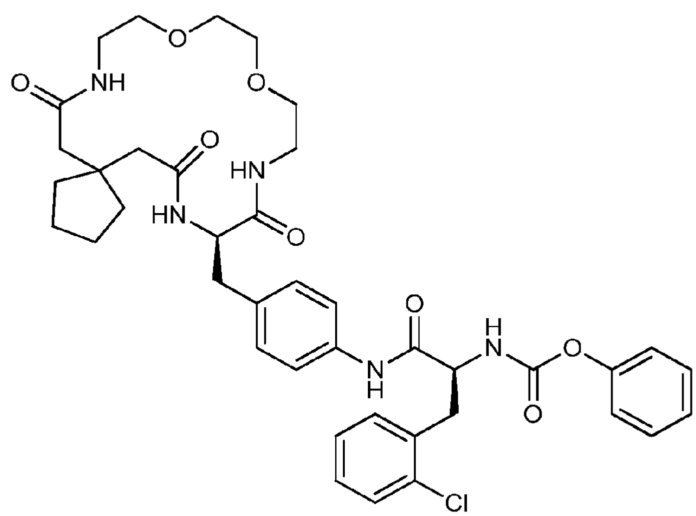
Compound No.	Structure
570	
571	

FIG. 12-219

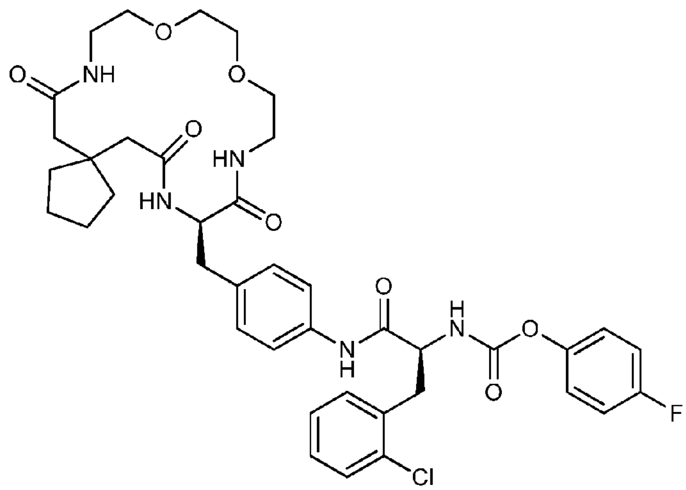
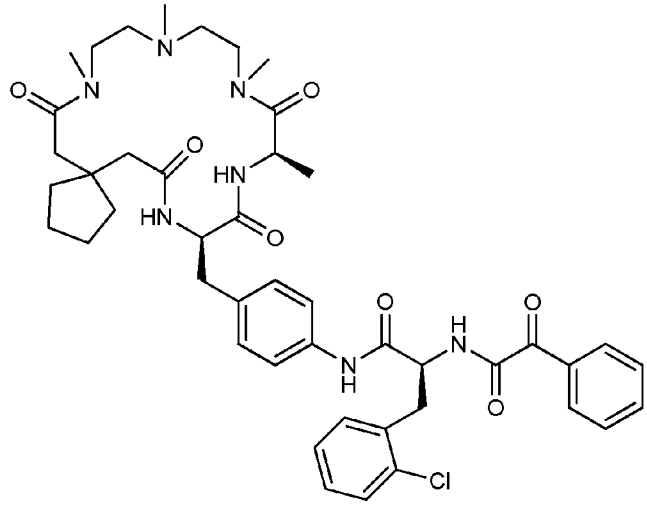
Compound No.	Structure
572	
573	

FIG. 12-220

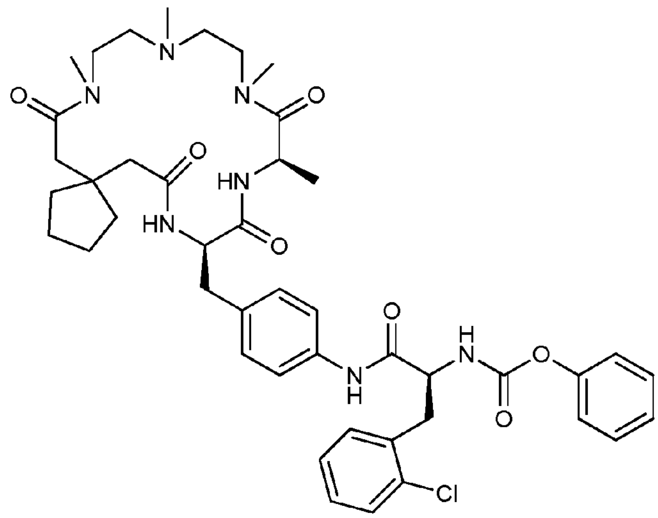
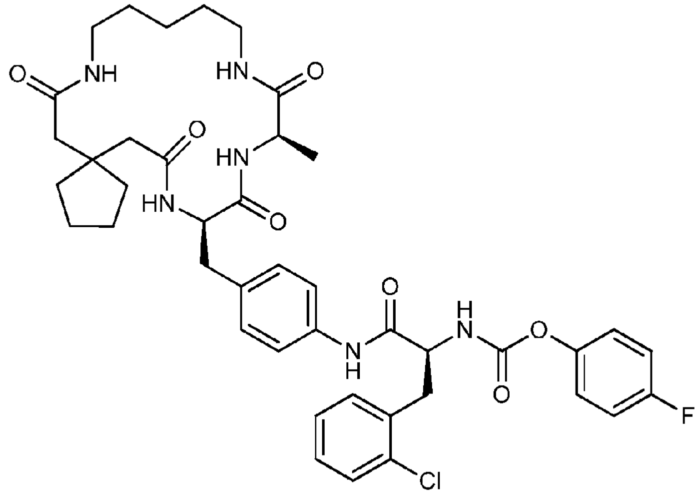
Compound No.	Structure
574	
575	

FIG. 12-221

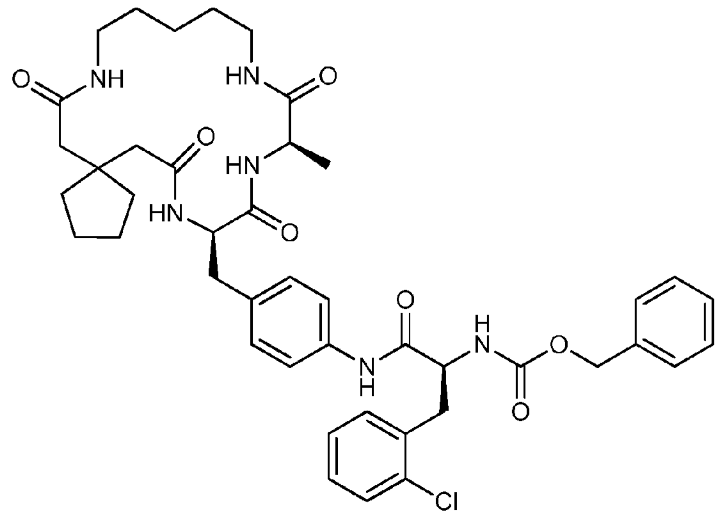
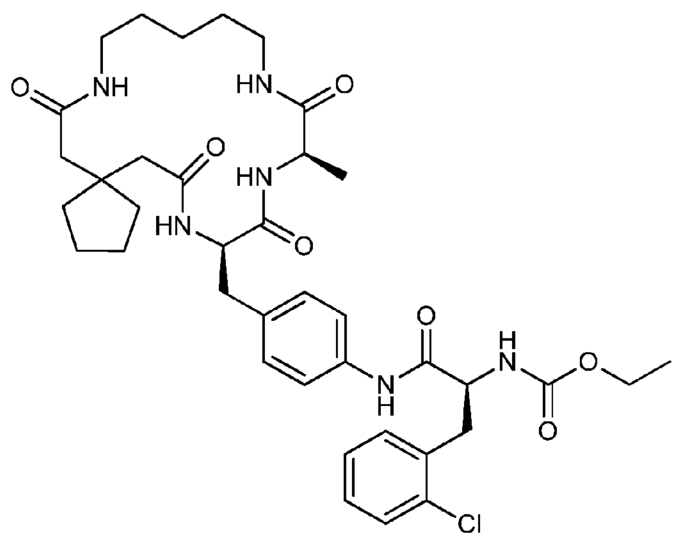
Compound No.	Structure
576	
577	

FIG. 12-222

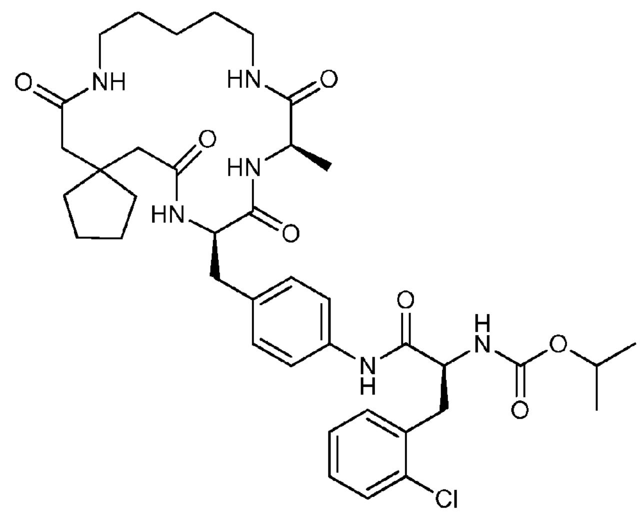
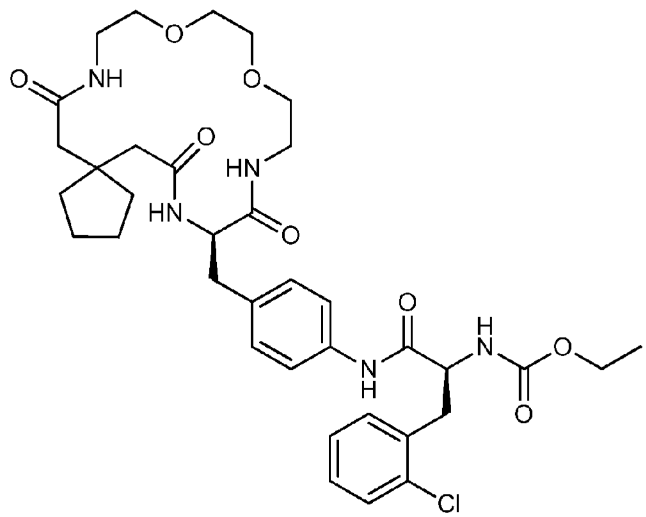
Compound No.	Structure
578	
579	

FIG. 12-223

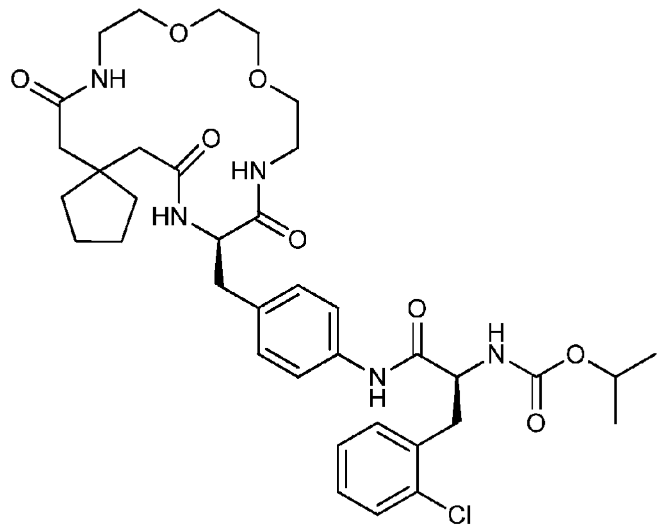
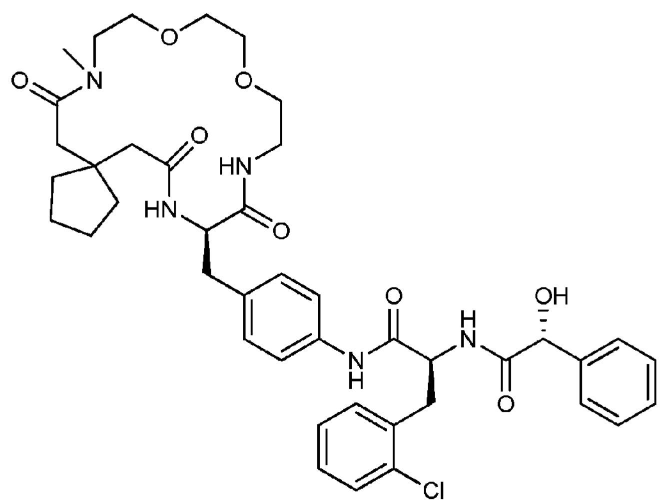
Compound No.	Structure
580	
581	

FIG. 12-224

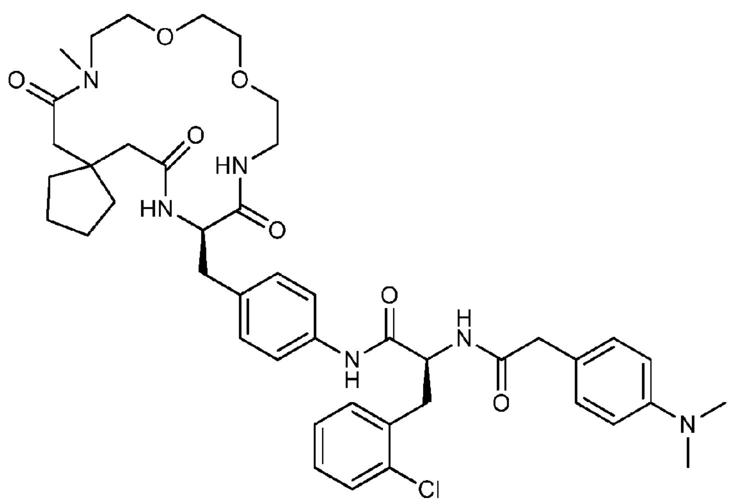
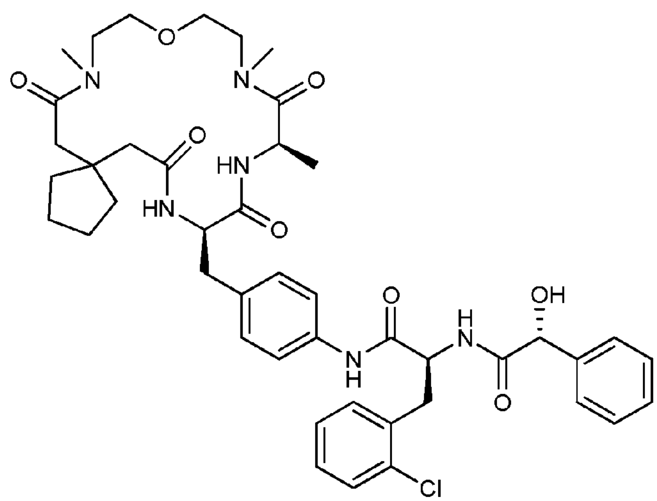
Compound No.	Structure
582	
583	

FIG. 12-225

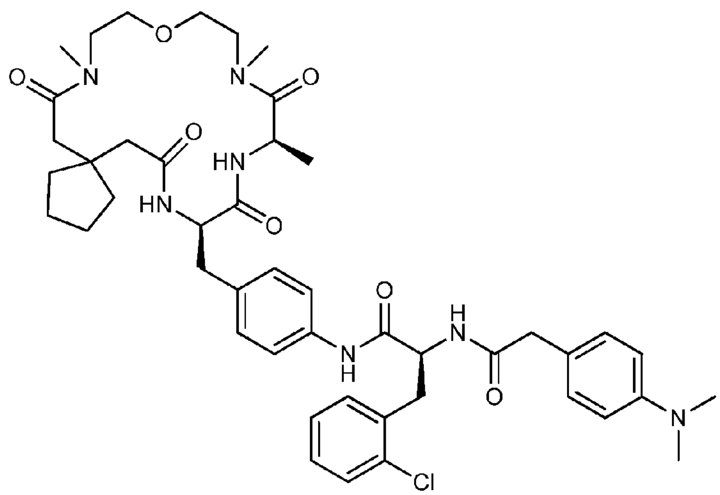
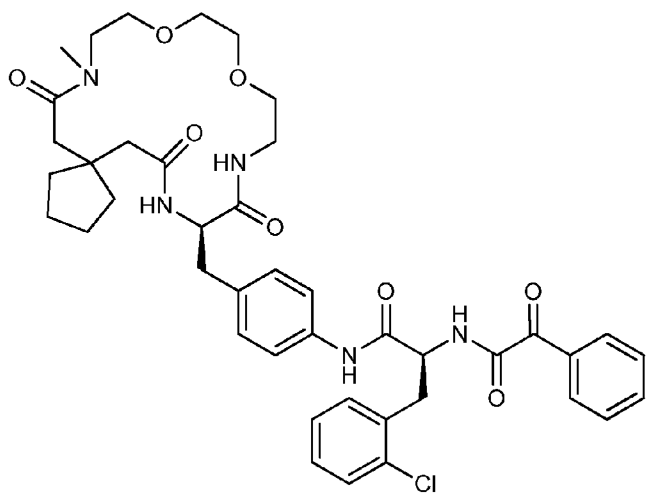
Compound No.	Structure
584	
585	

FIG. 12-226

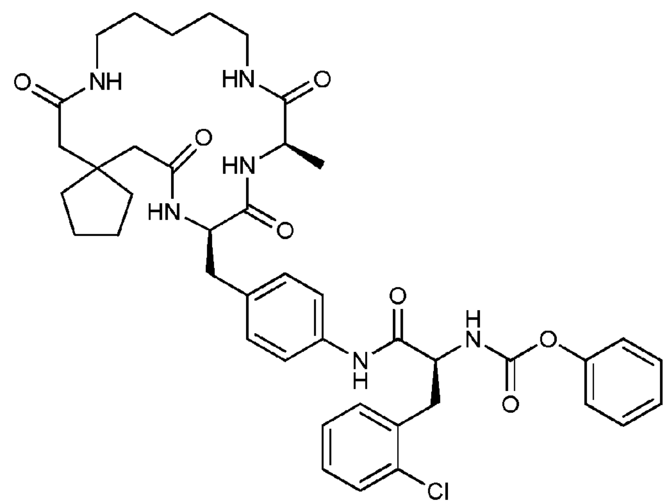
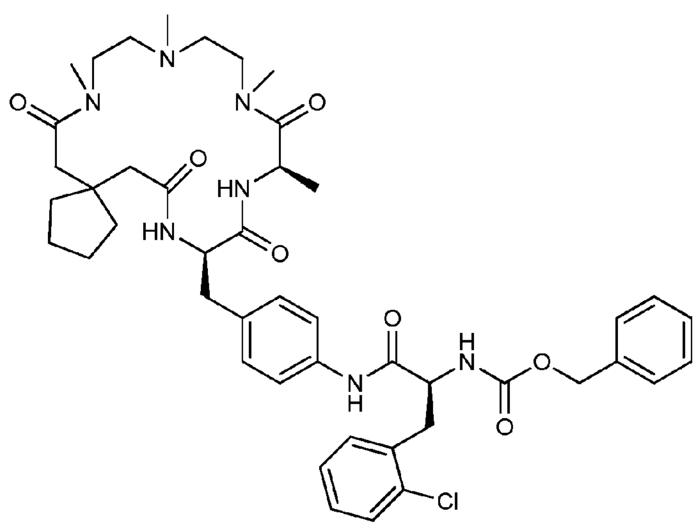
Compound No.	Structure
586	
587	

FIG. 12-227

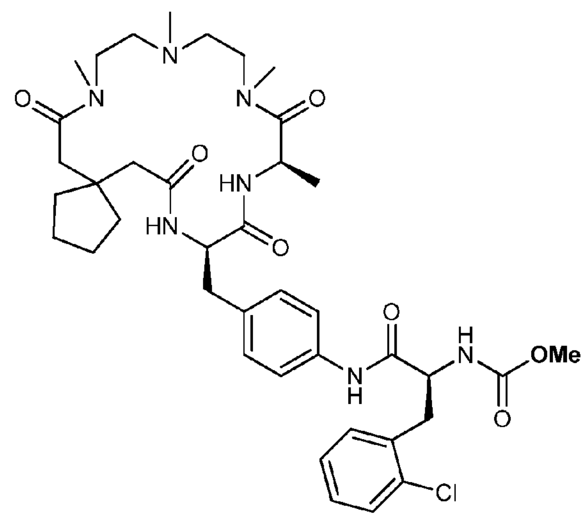
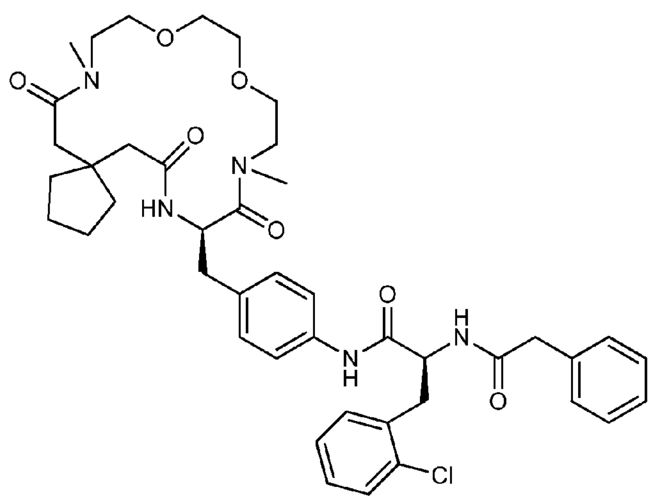
Compound No.	Structure
588	
589	

FIG. 12-228

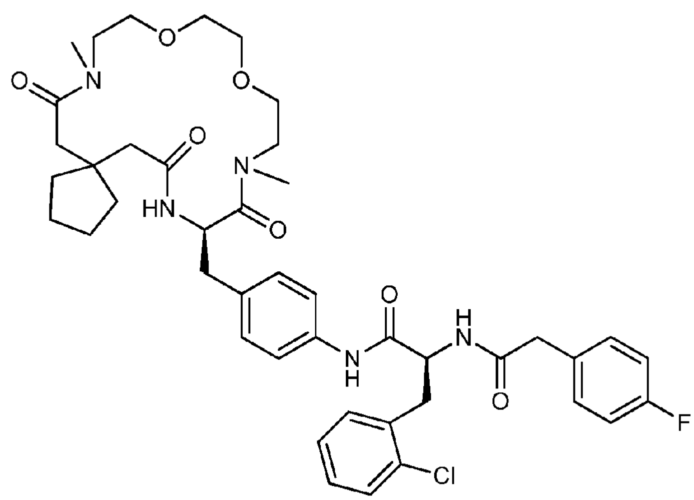
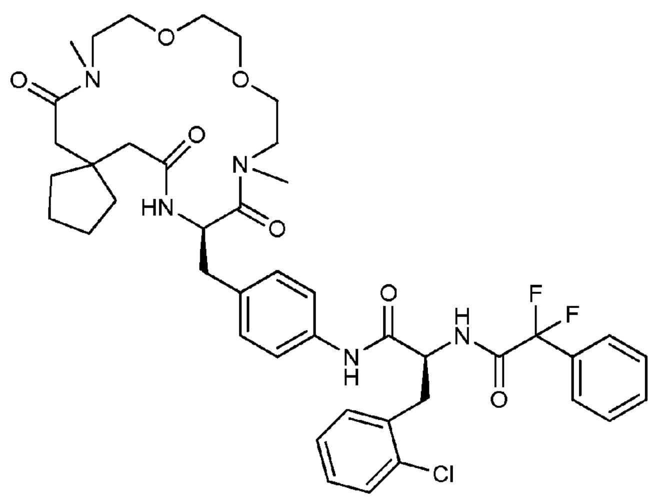
Compound No.	Structure
590	
591	

FIG. 12-229

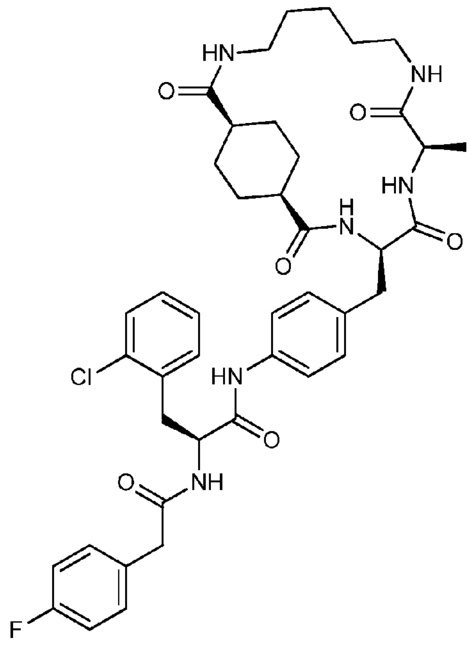
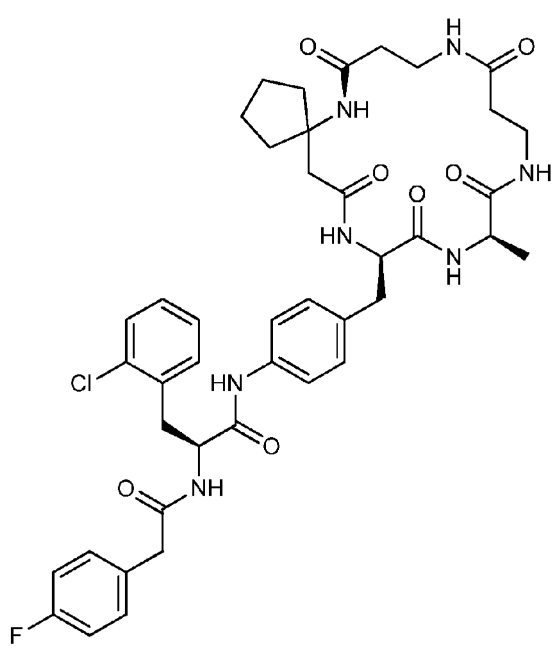
Compound No.	Structure
592	
593	

FIG. 12-230

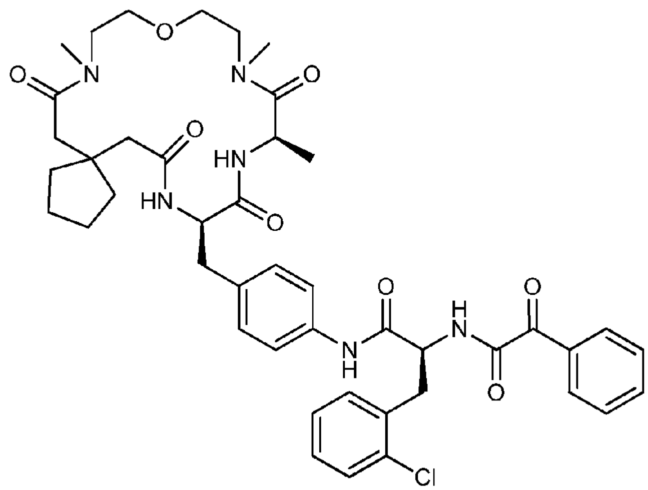
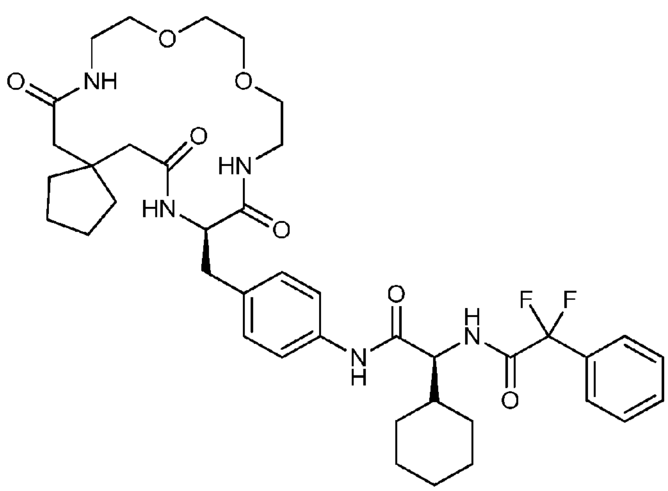
Compound No.	Structure
594	
595	

FIG. 12-231

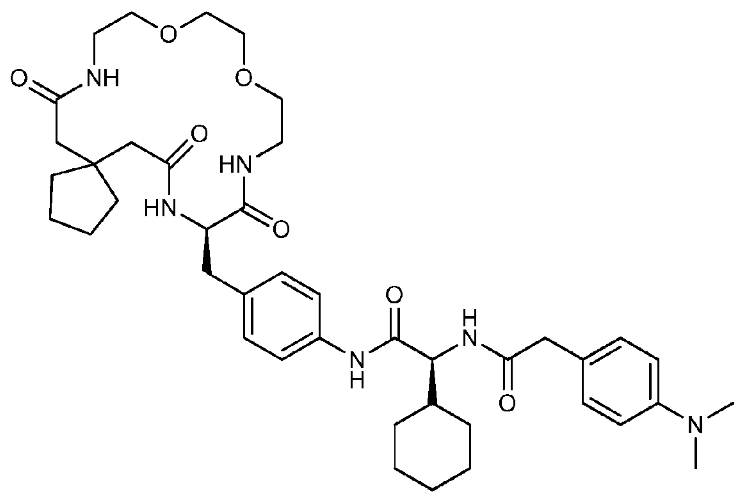
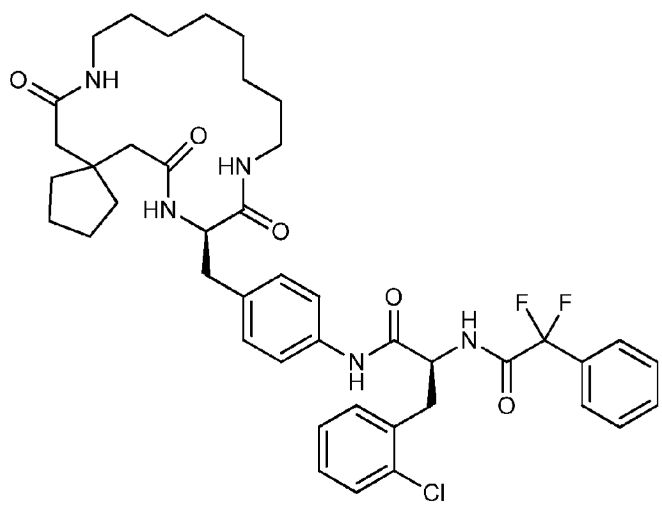
Compound No.	Structure
596	
597	

FIG. 12-232

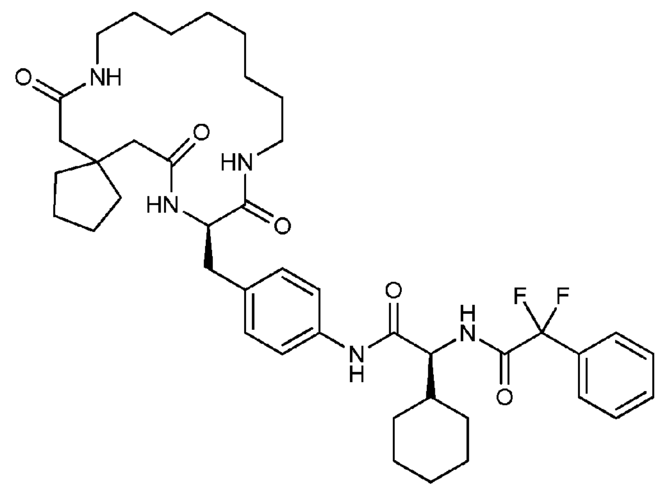
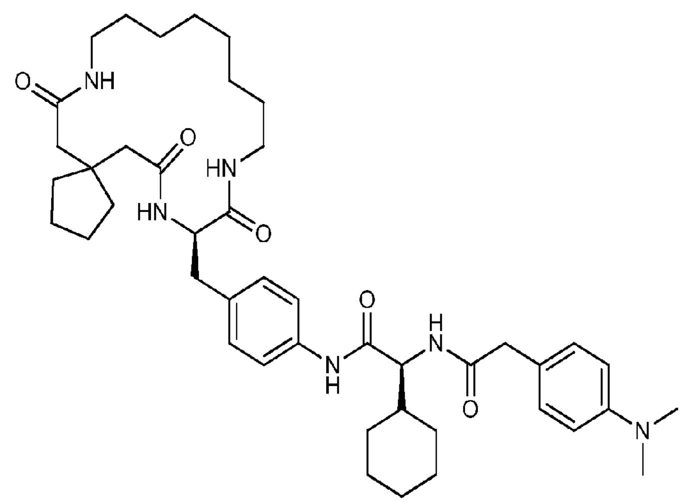
Compound No.	Structure
598	
599	

FIG. 12-233

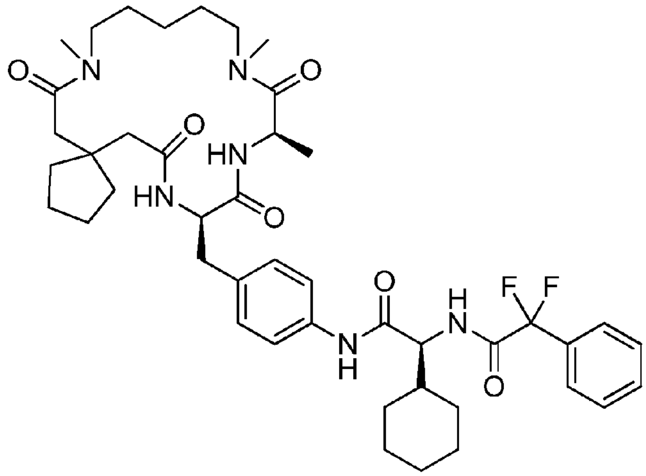
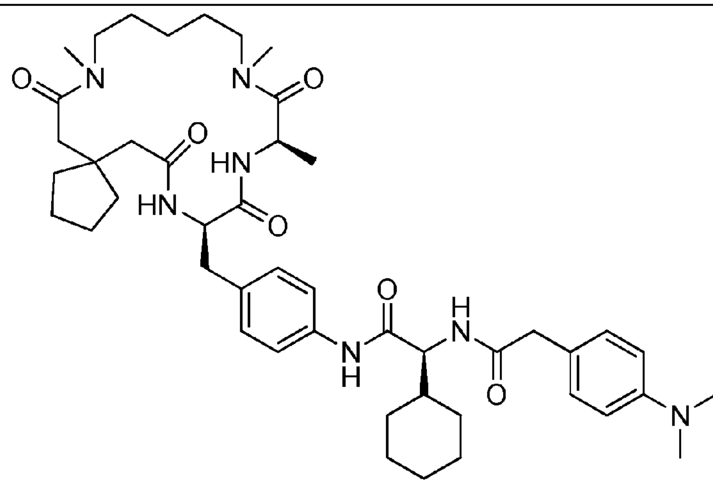
Compound No.	Structure
600	
601	

FIG. 12-234

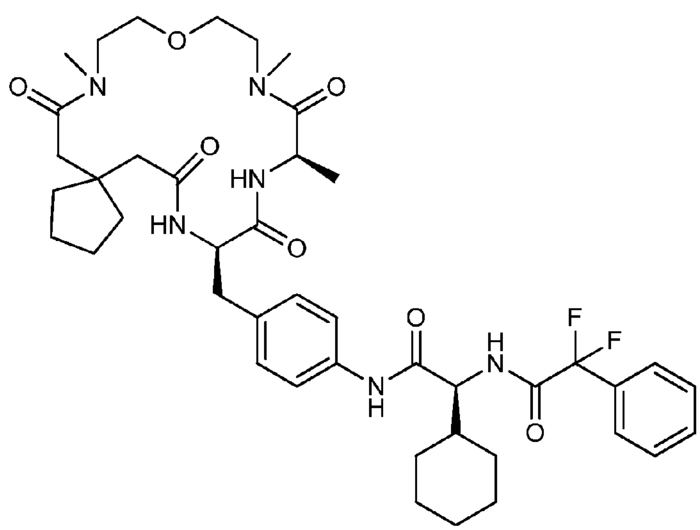
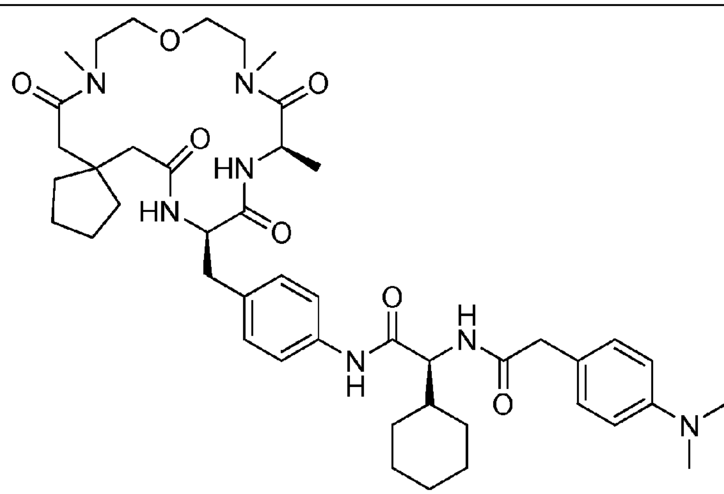
Compound No.	Structure
602	
603	

FIG. 12-235

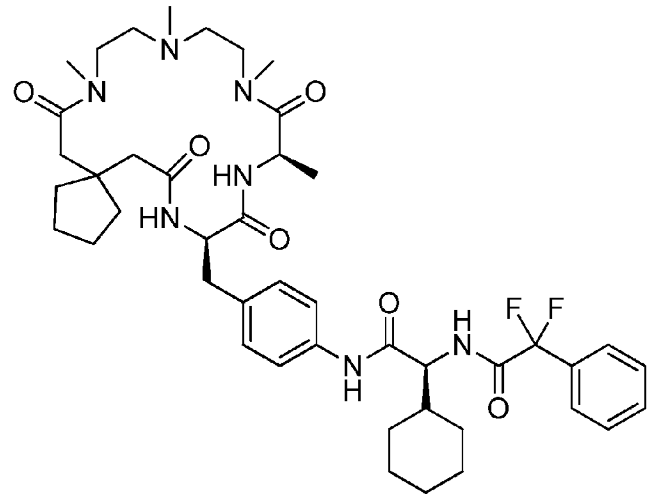
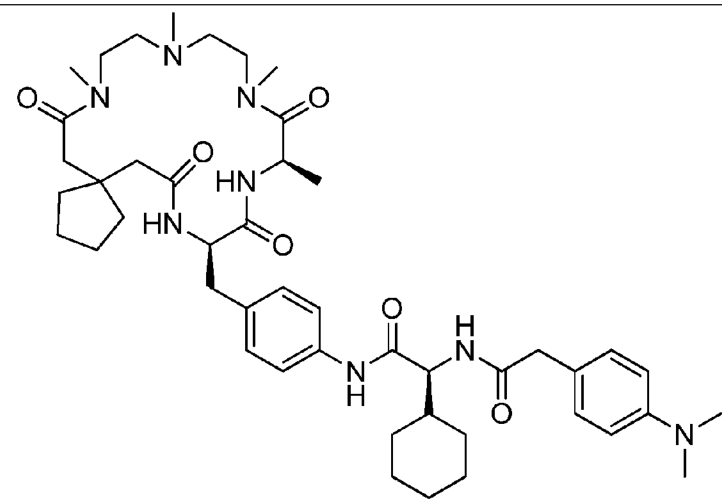
Compound No.	Structure
604	
605	

FIG. 12-236

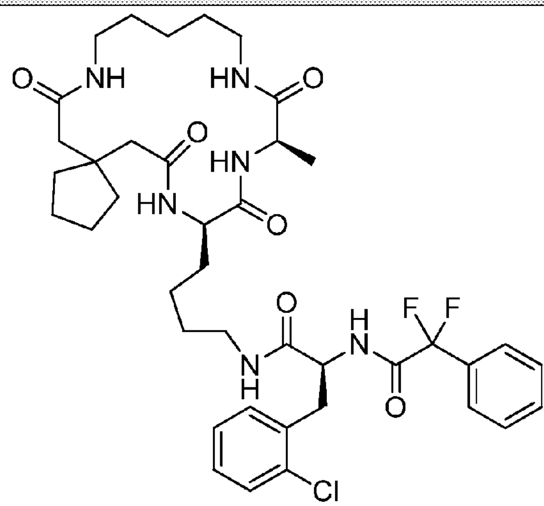
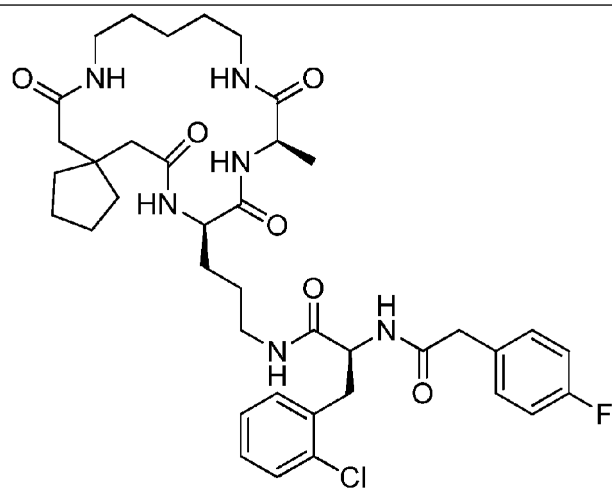
Compound No.	Structure
606	
607	

FIG. 12-237

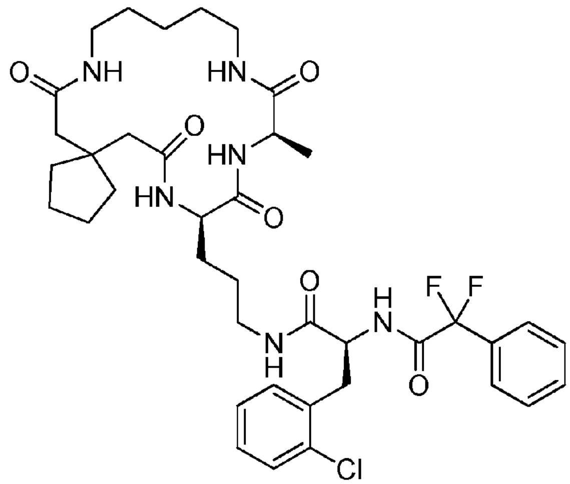
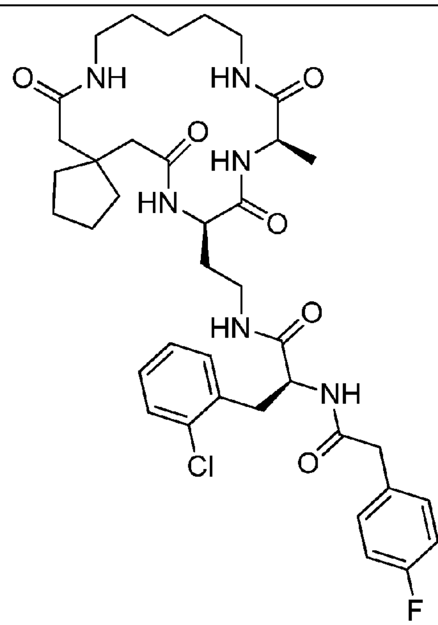
Compound No.	Structure
608	
609	

FIG. 12-238

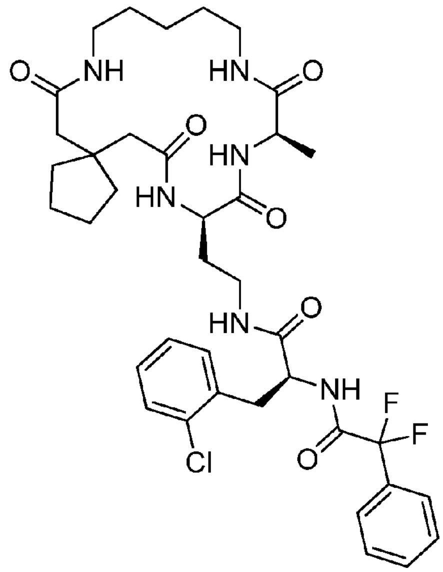
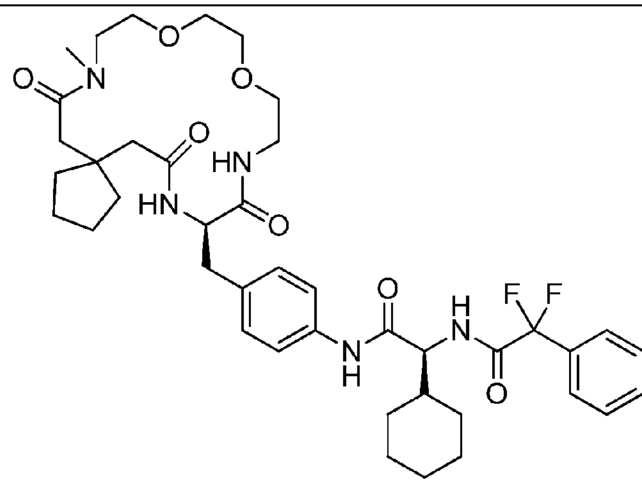
Compound No.	Structure
610	
611	

FIG. 12-239

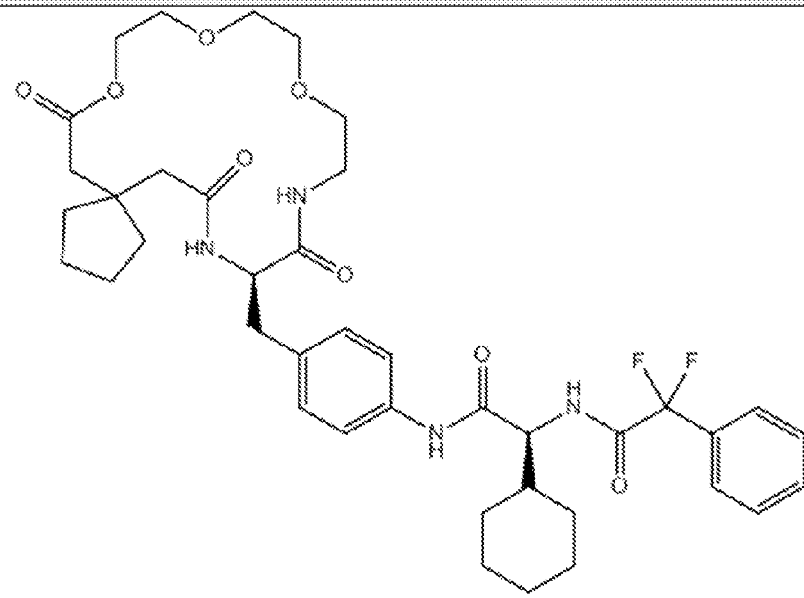
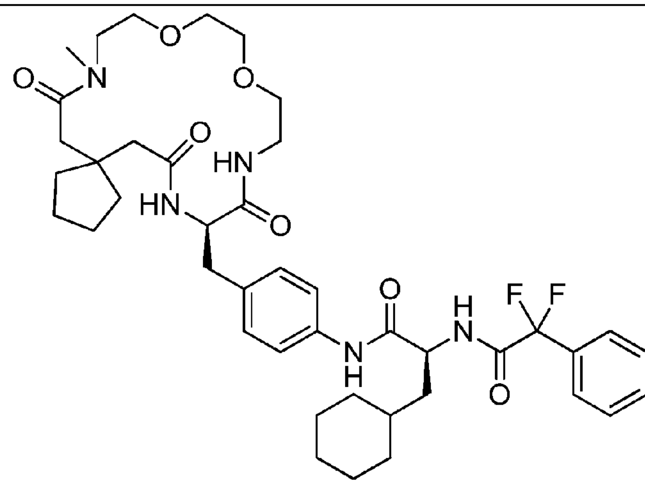
Compound No.	Structure
612	
613	

FIG. 12-240

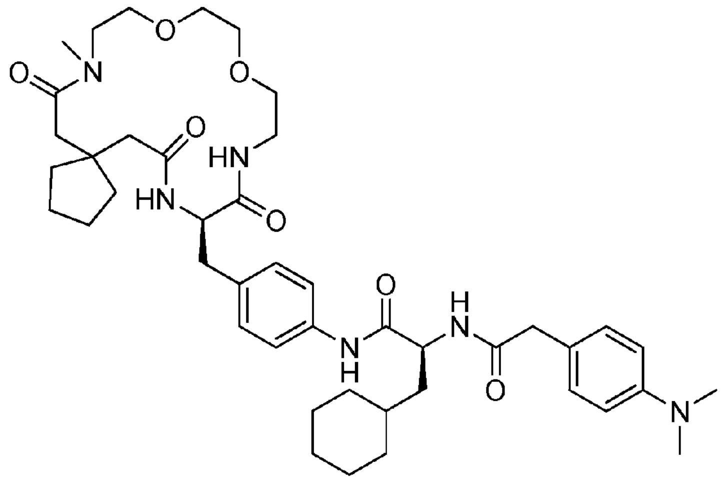
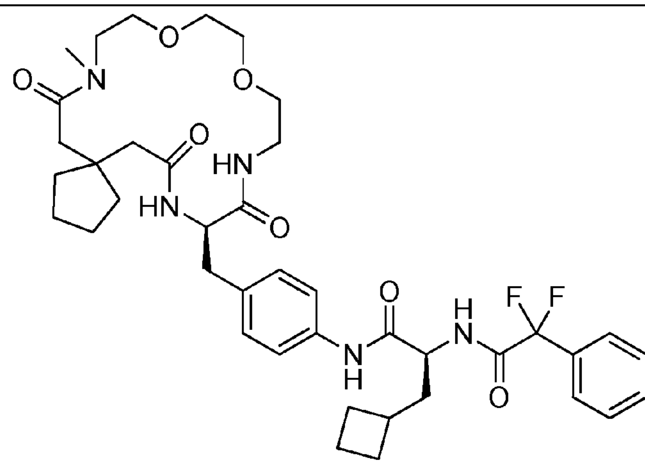
Compound No.	Structure
614	
615	

FIG. 12-241

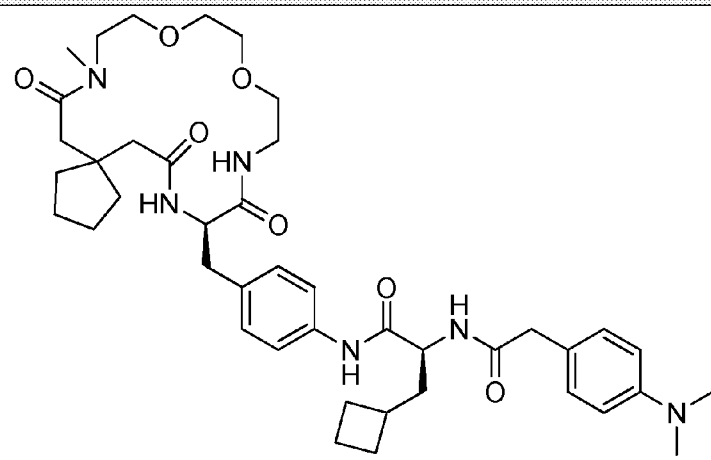
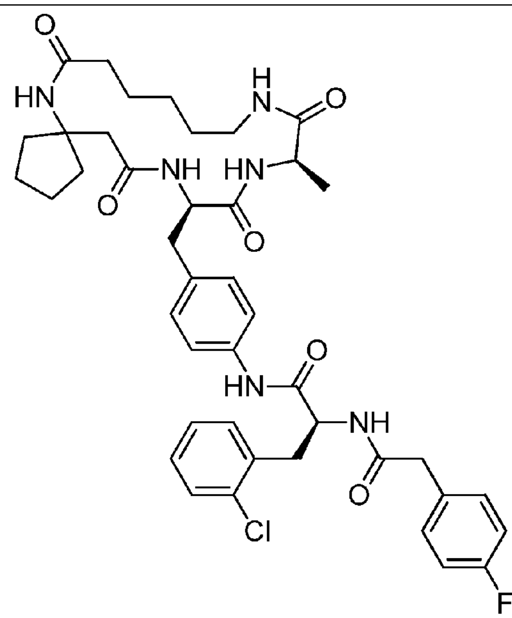
Compound No.	Structure
616	
617	

FIG. 12-242

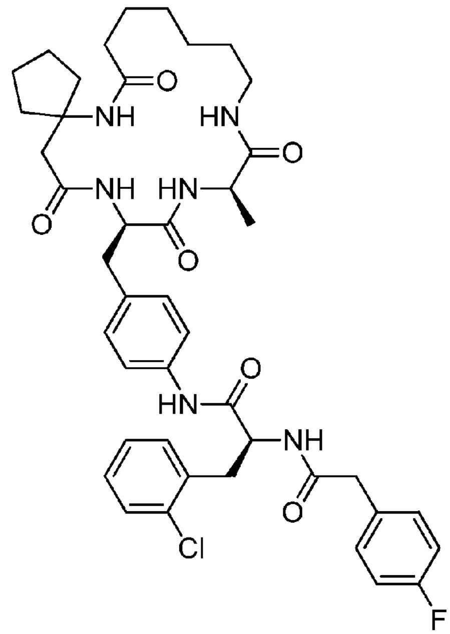
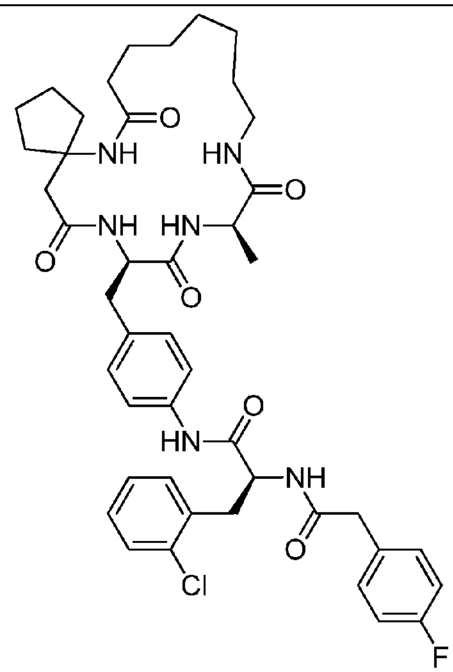
Compound No.	Structure
618	
619	

FIG. 12-243

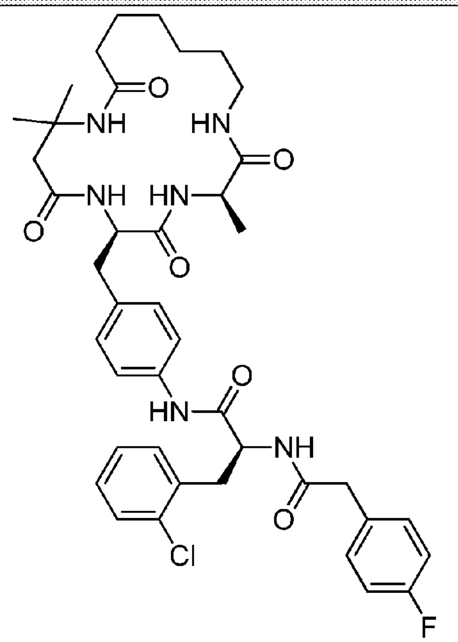
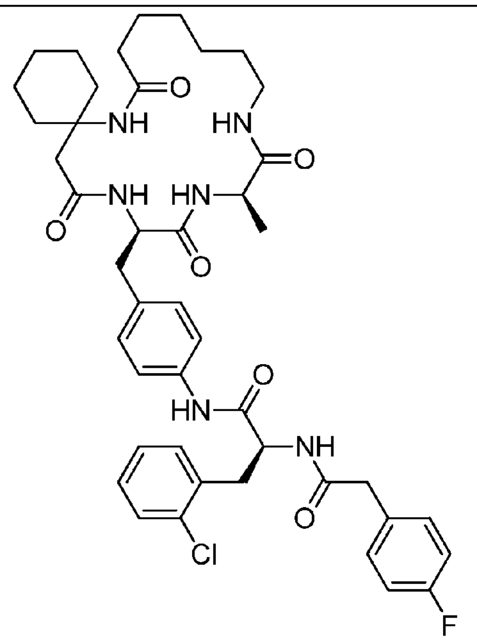
Compound No.	Structure
620	
621	

FIG. 12-244

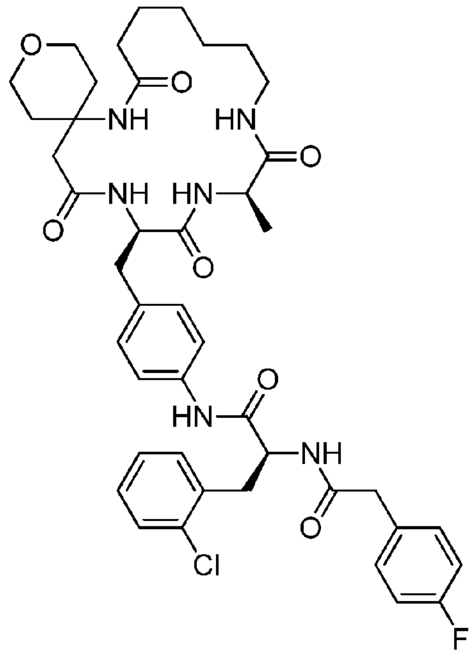
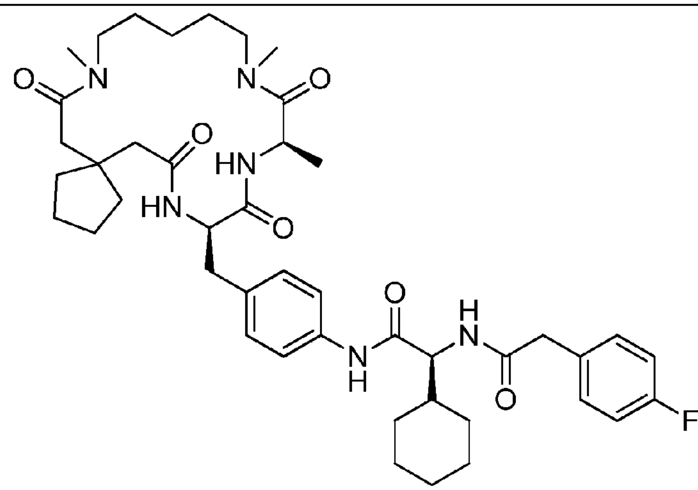
Compound No.	Structure
622	
623	

FIG. 12-245

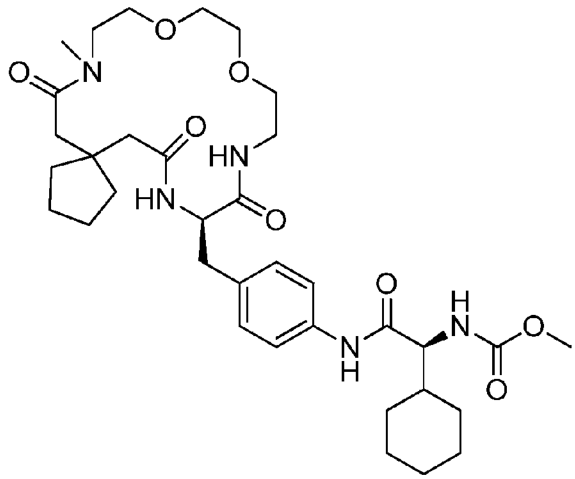
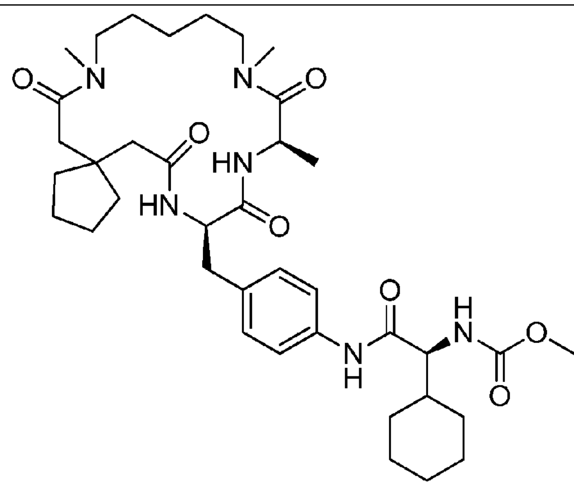
Compound No.	Structure
624	
625	

FIG. 12-246

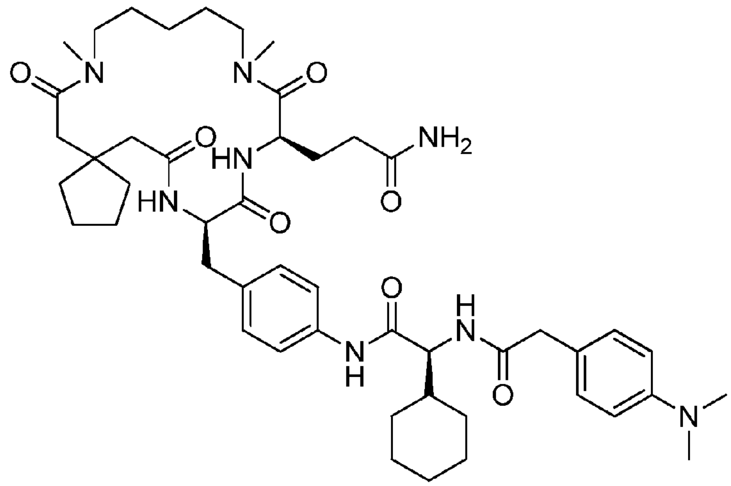
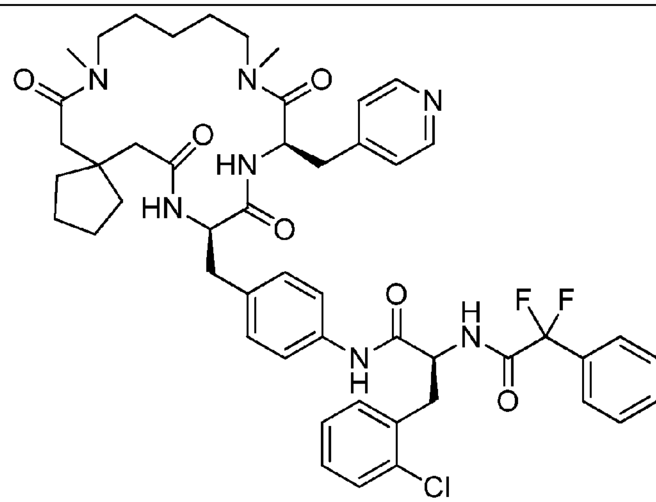
Compound No.	Structure
626	
627	

FIG. 12-247

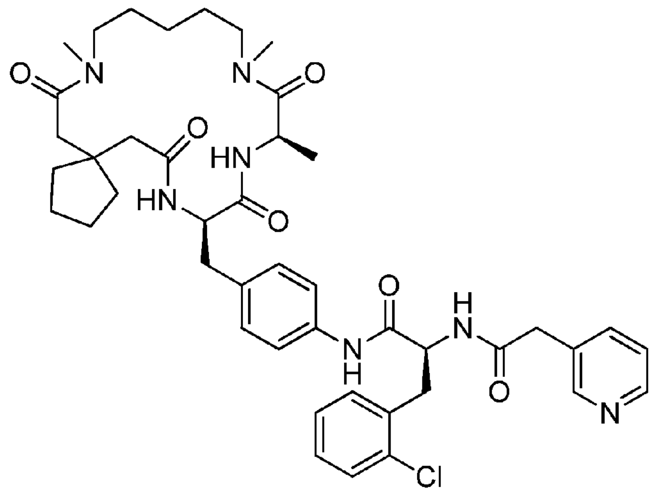
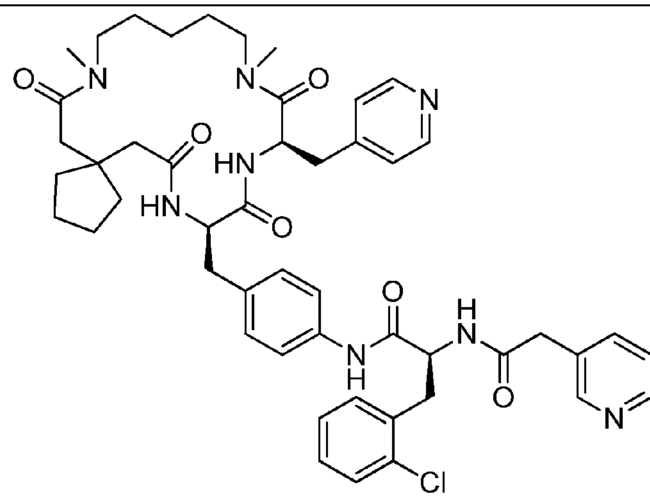
Compound No.	Structure
628	
629	

FIG. 12-248

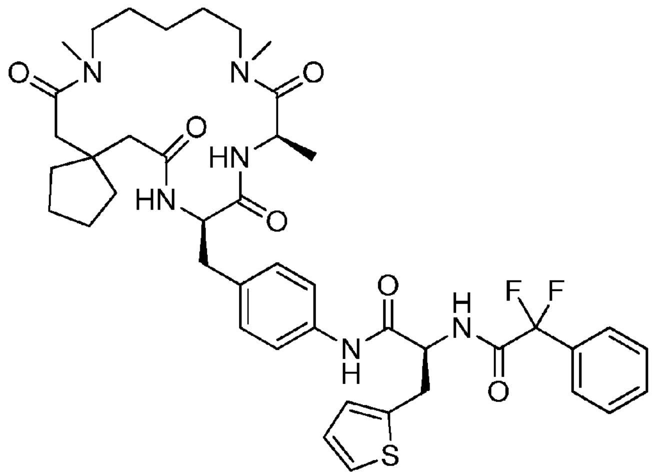
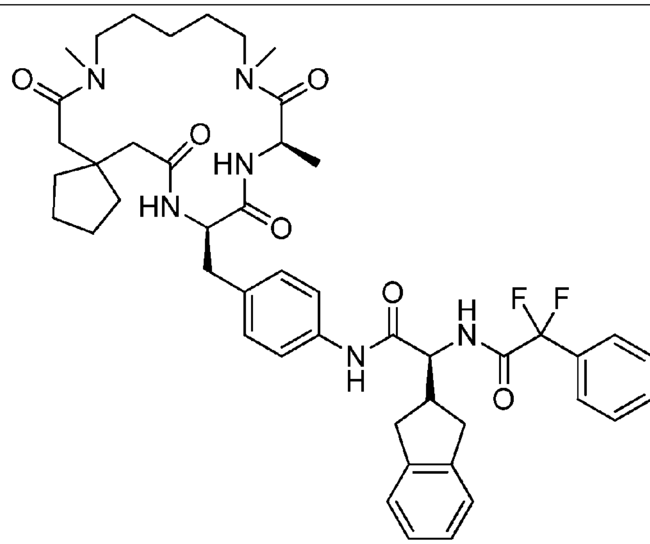
Compound No.	Structure
630	
631	

FIG. 12-249

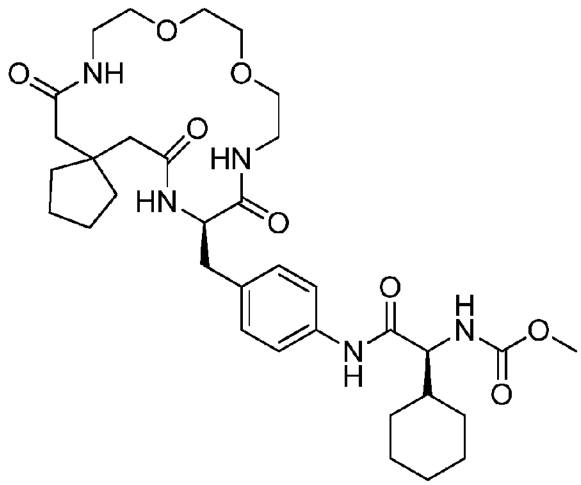
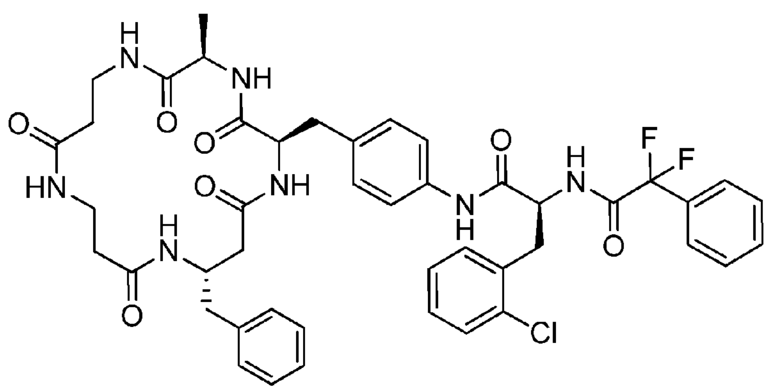
Compound No.	Structure
632	
633	

FIG. 12-250

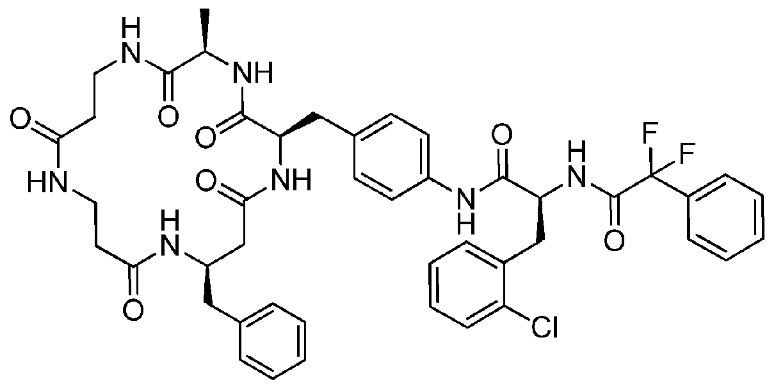
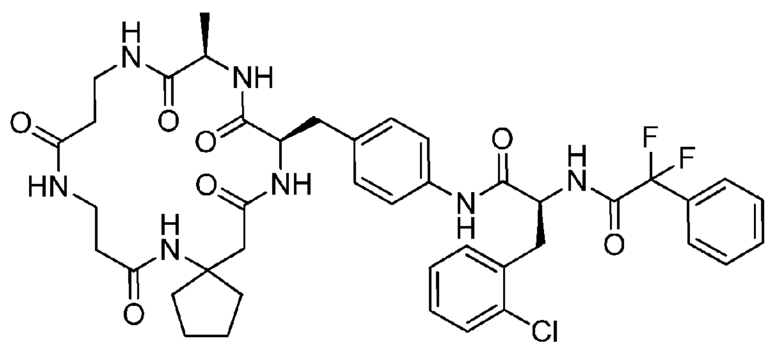
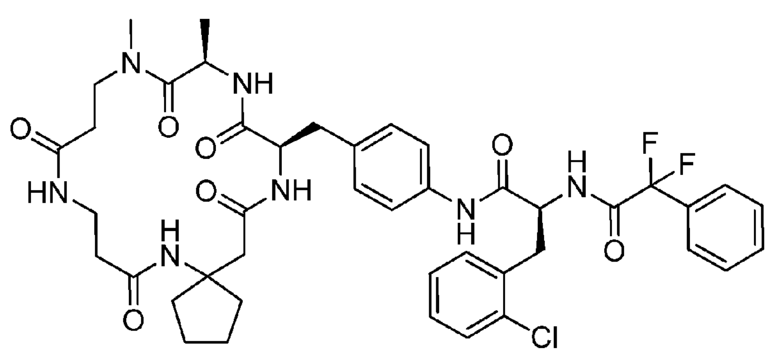
Compound No.	Structure
634	
635	
636	

FIG. 12-251

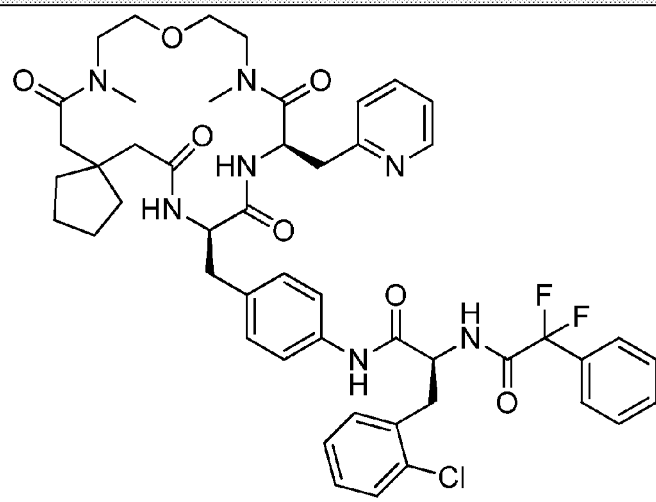
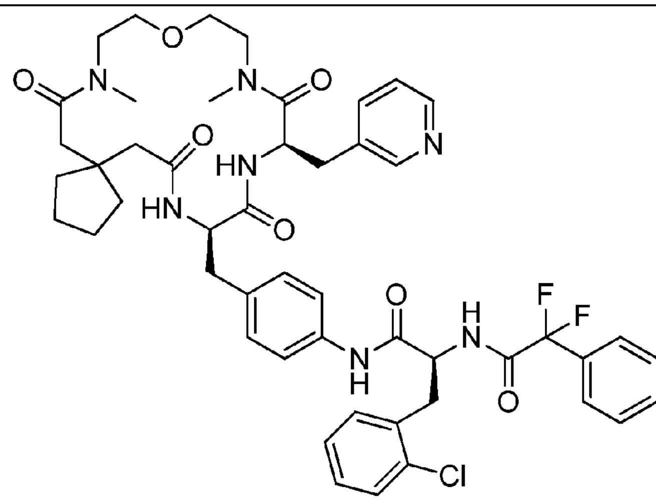
Compound No.	Structure
637	
638	

FIG. 12-252

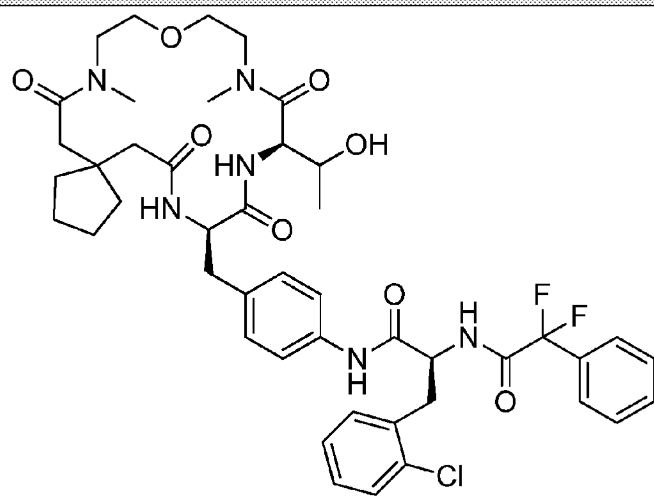
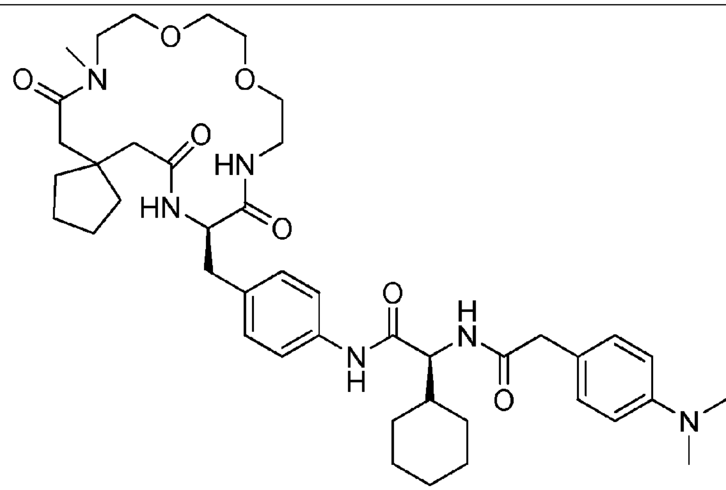
Compound No.	Structure
639	
640	

FIG. 12-253

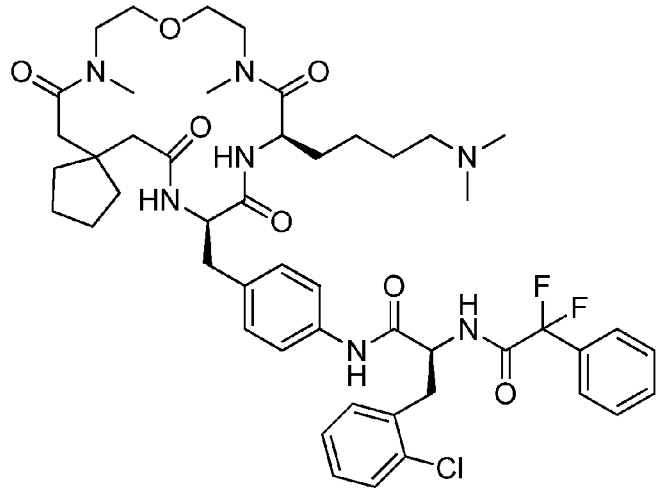
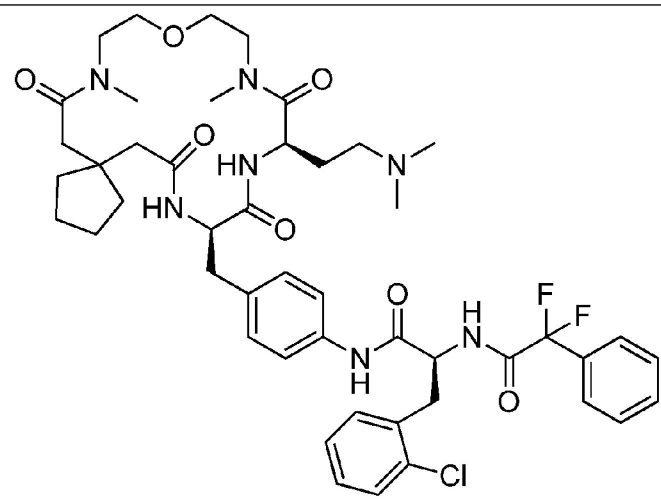
Compound No.	Structure
641	
642	

FIG. 12-254

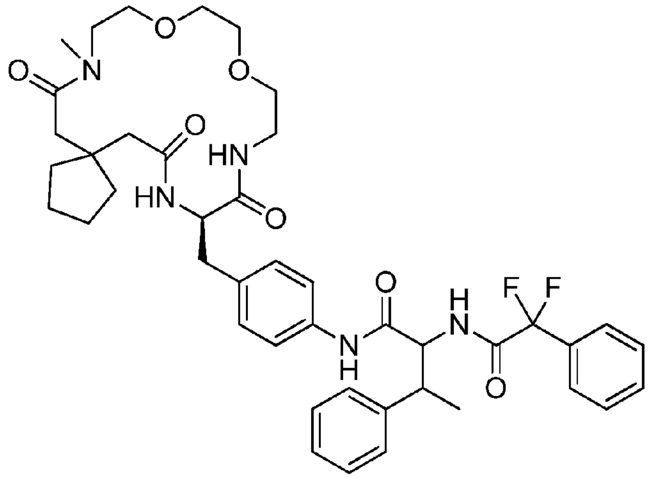
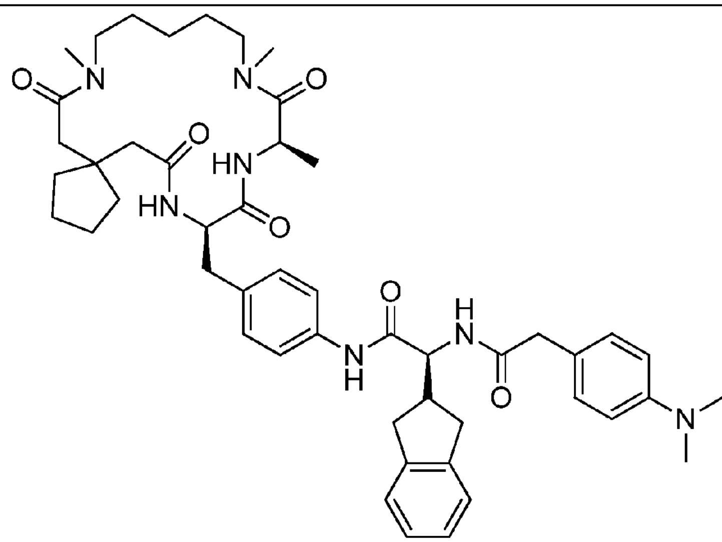
Compound No.	Structure
643	
644	

FIG. 12-255

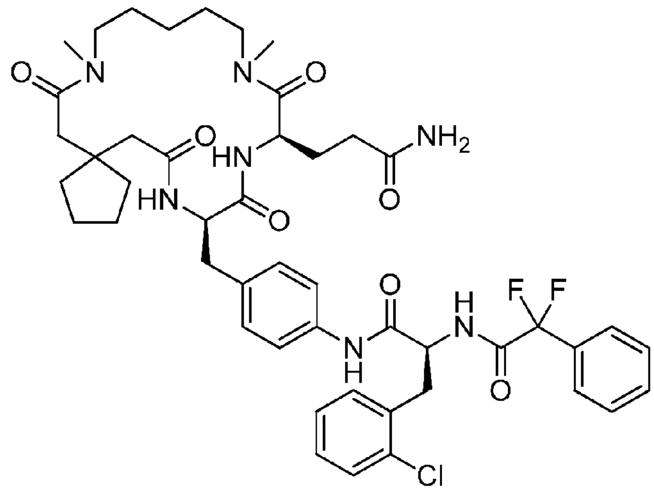
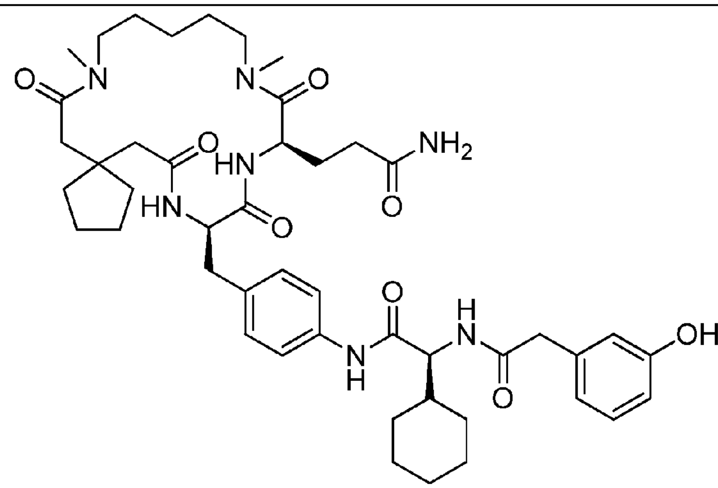
Compound No.	Structure
645	
646	

FIG. 12-256

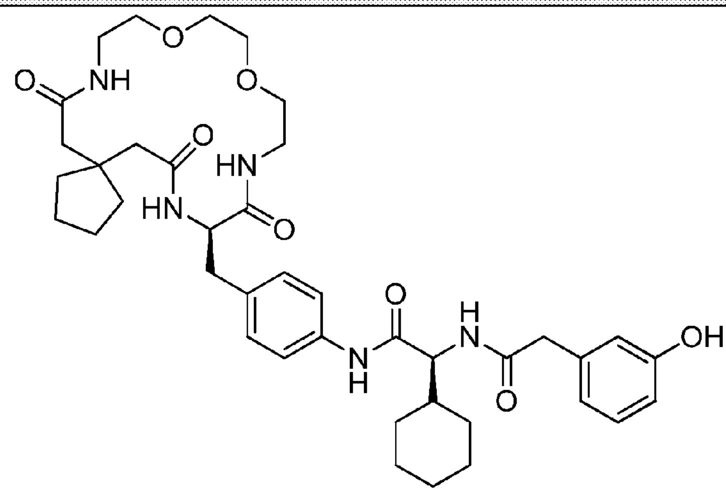
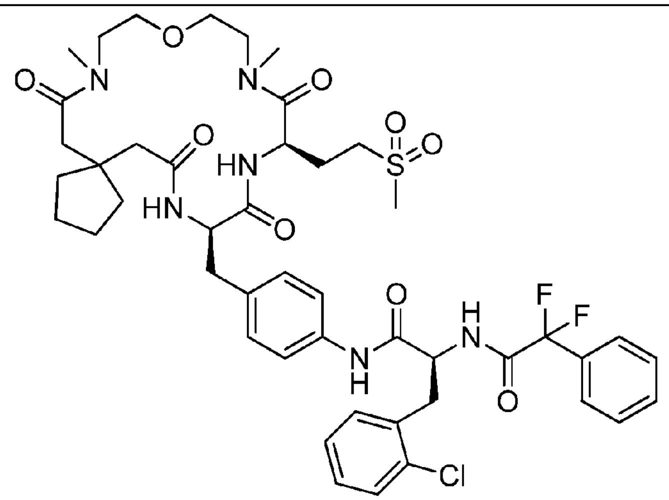
Compound No.	Structure
647	
649	

FIG. 12-257

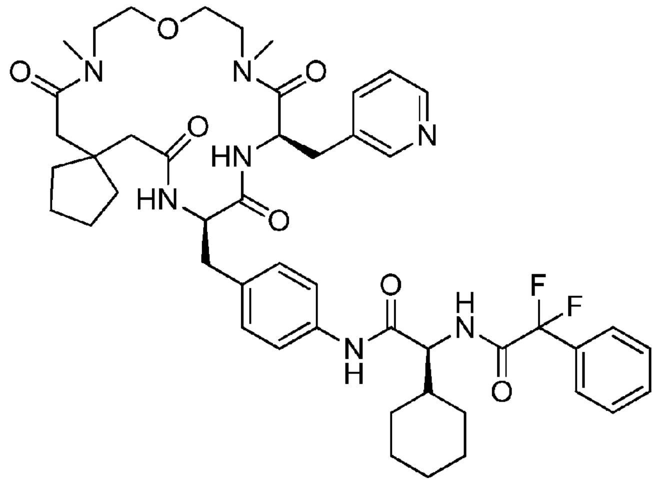
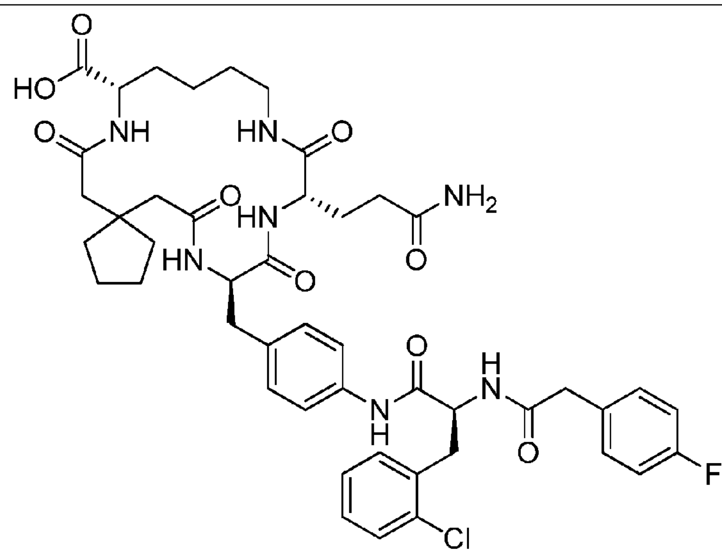
Compound No.	Structure
650	
651	

FIG. 12-258

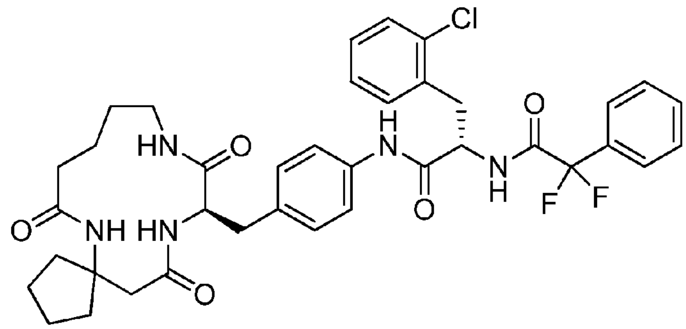
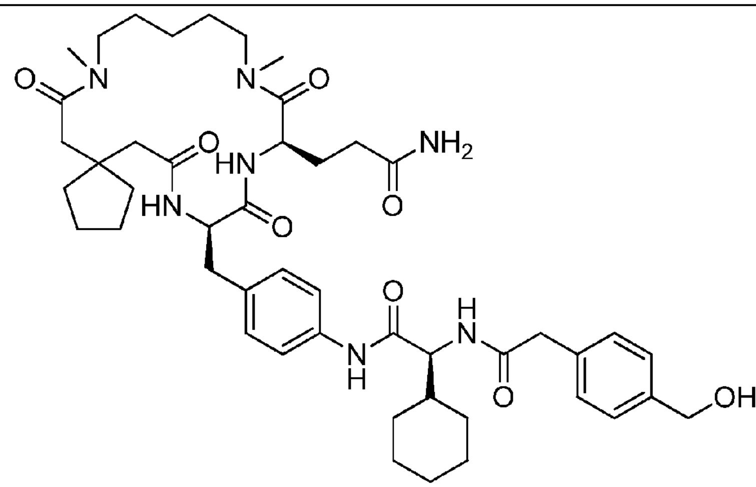
Compound No.	Structure
652	
653	

FIG. 12-259

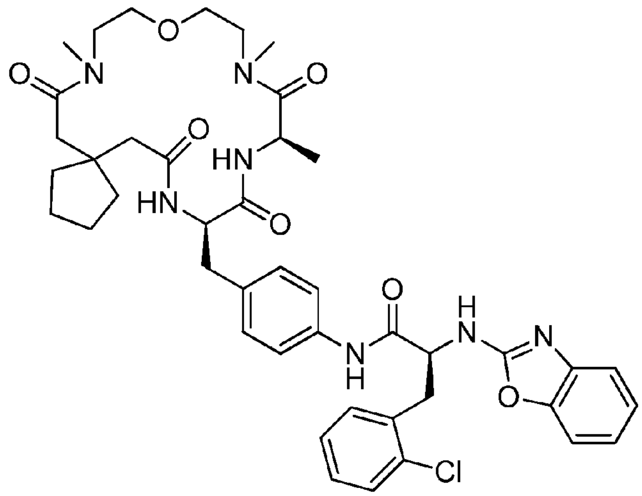
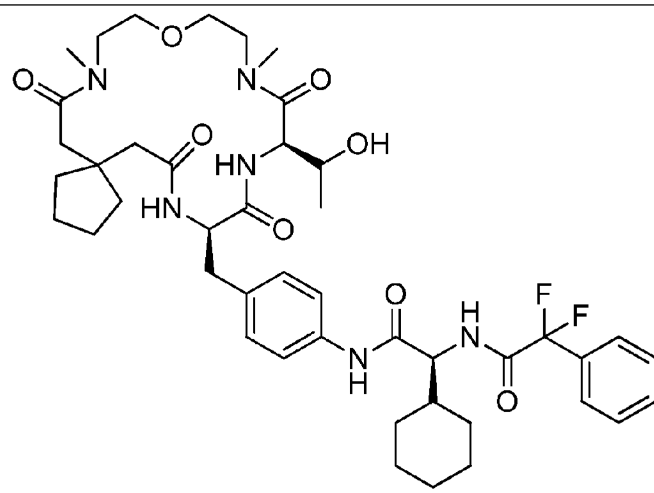
Compound No.	Structure
654	
655	

FIG. 12-260

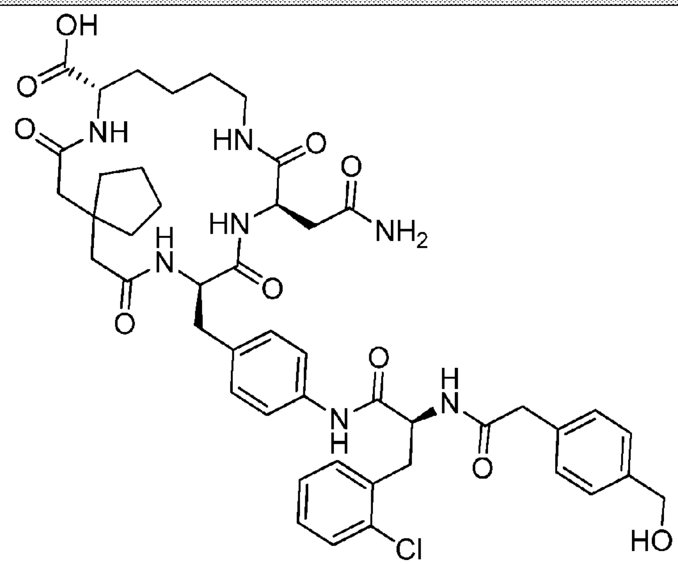
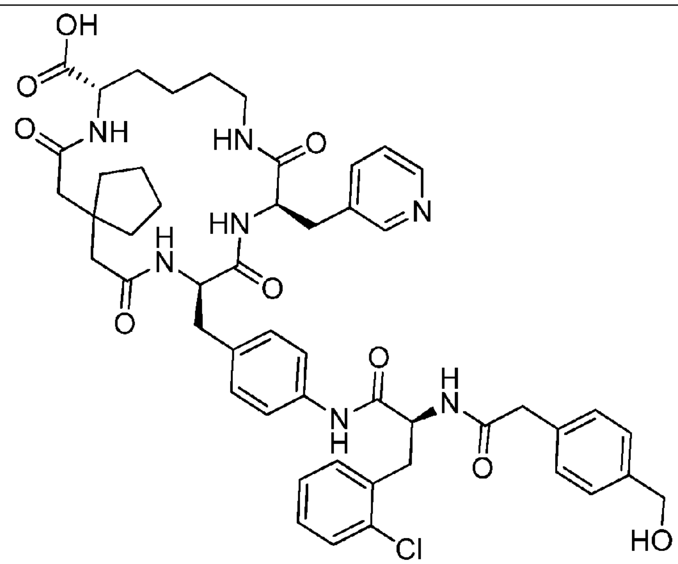
Compound No.	Structure
656	
657	

FIG. 12-261

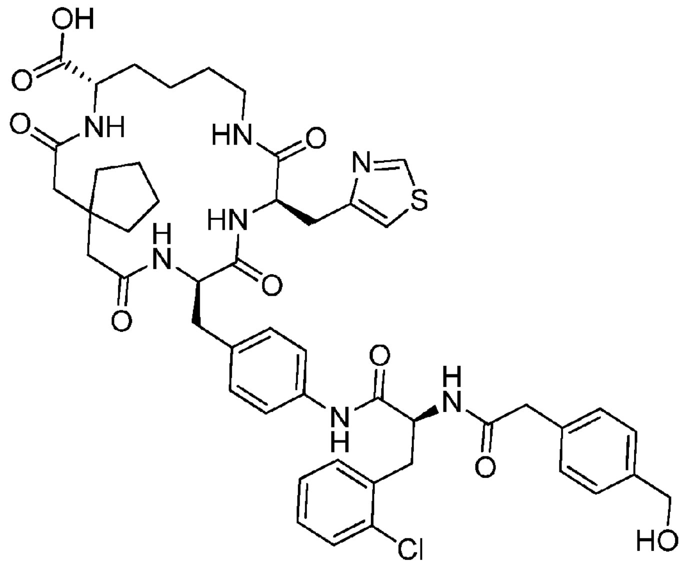
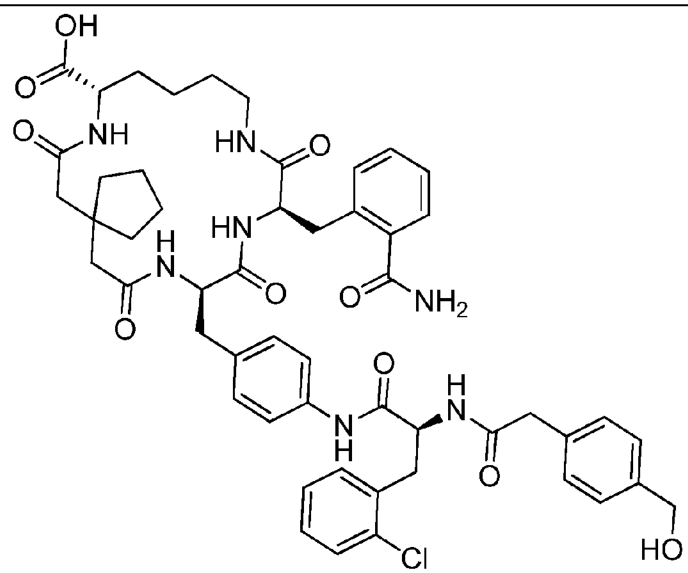
Compound No.	Structure
658	
659	

FIG. 12-262

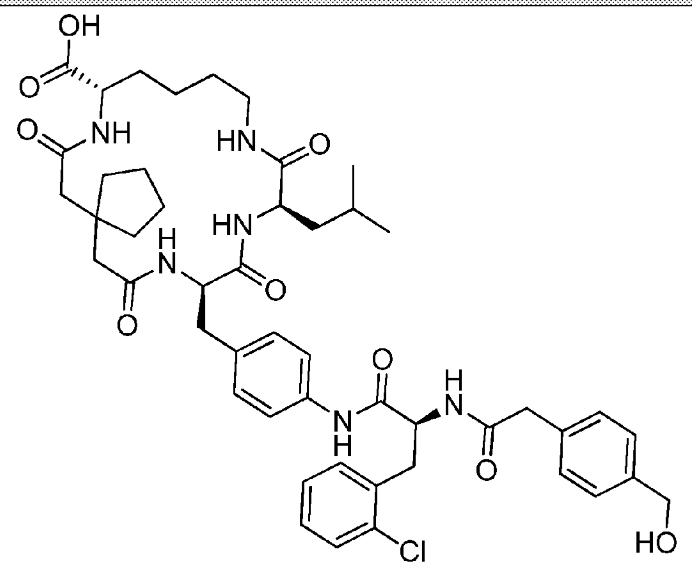
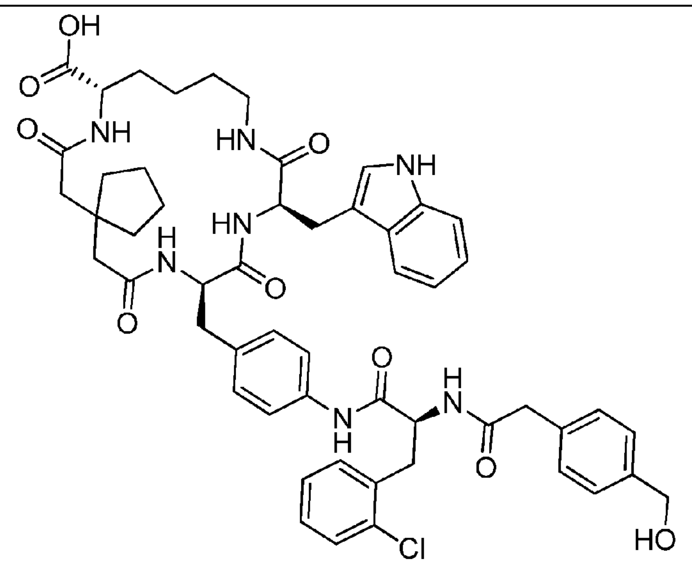
Compound No.	Structure
660	
661	

FIG. 12-263

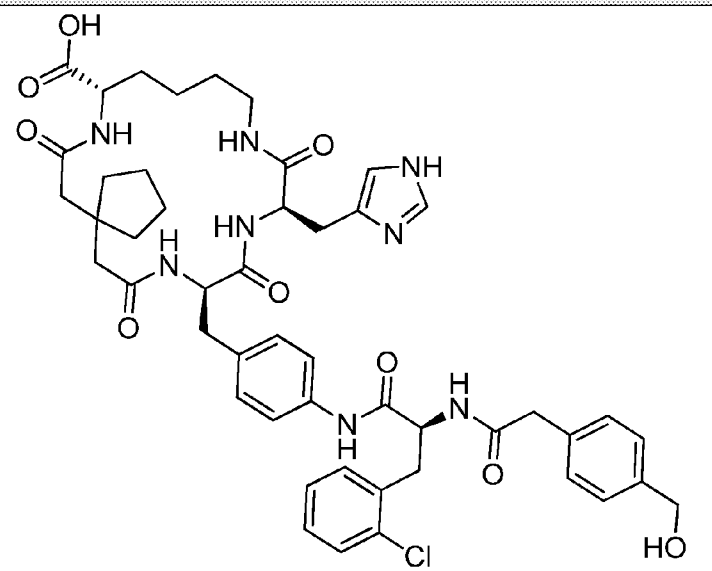
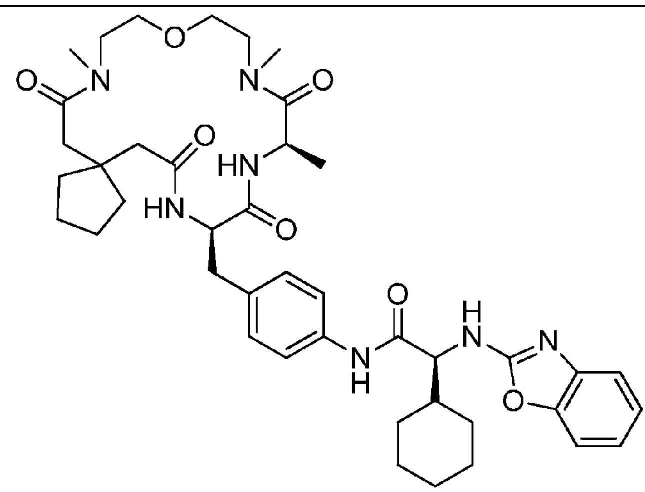
Compound No.	Structure
662	
663	

FIG. 12-264

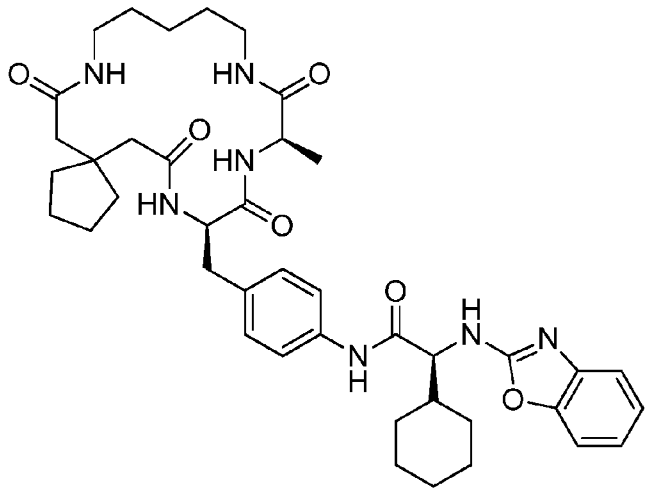
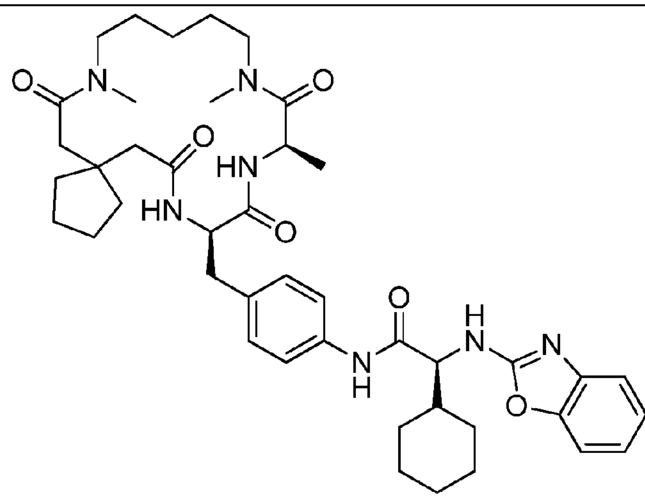
Compound No.	Structure
664	
665	

FIG. 12-265

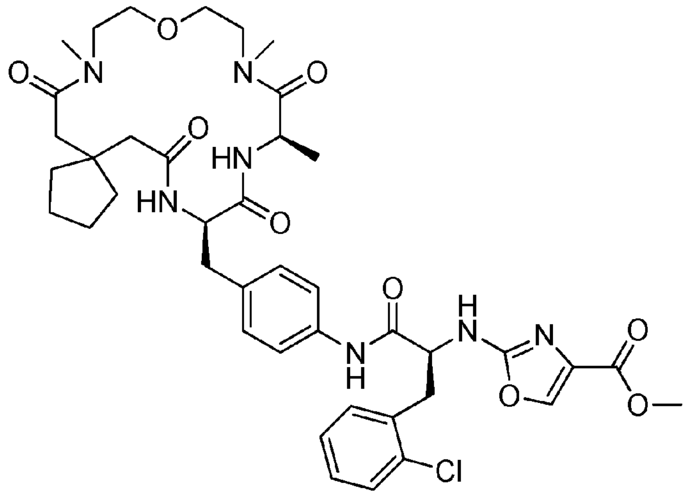
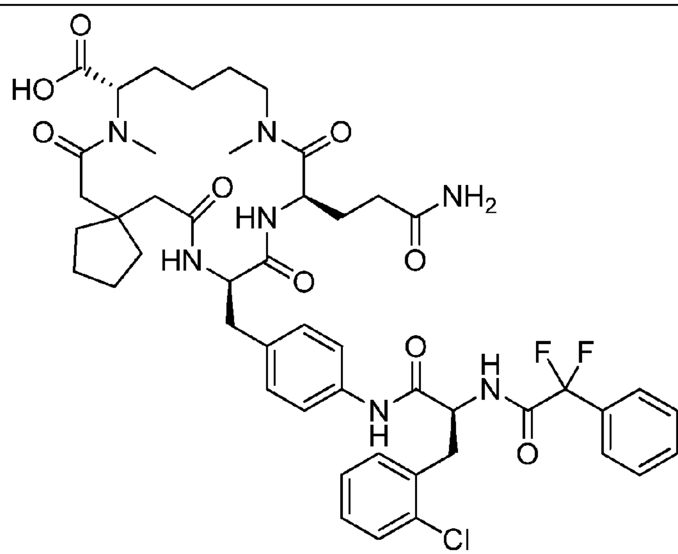
Compound No.	Structure
666	
667	

FIG. 12-266

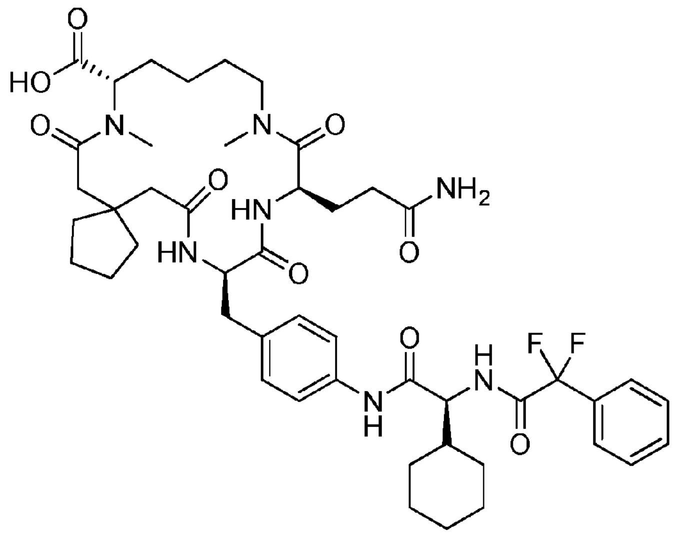
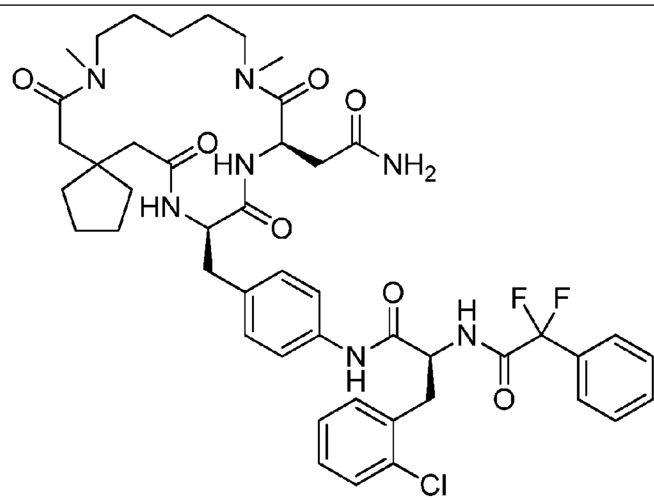
Compound No.	Structure
668	
669	

FIG. 12-267

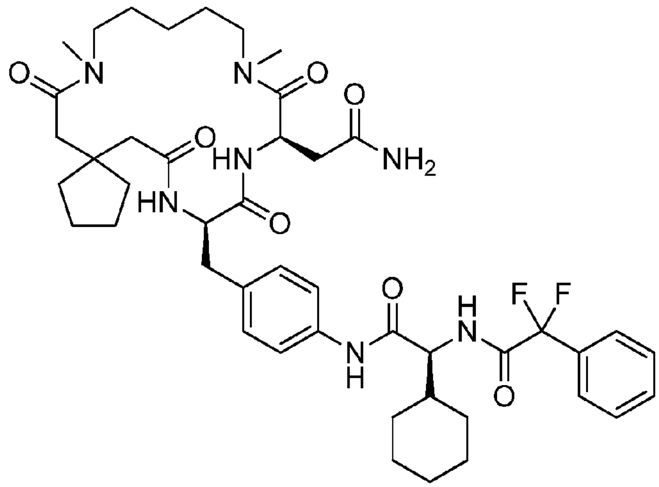
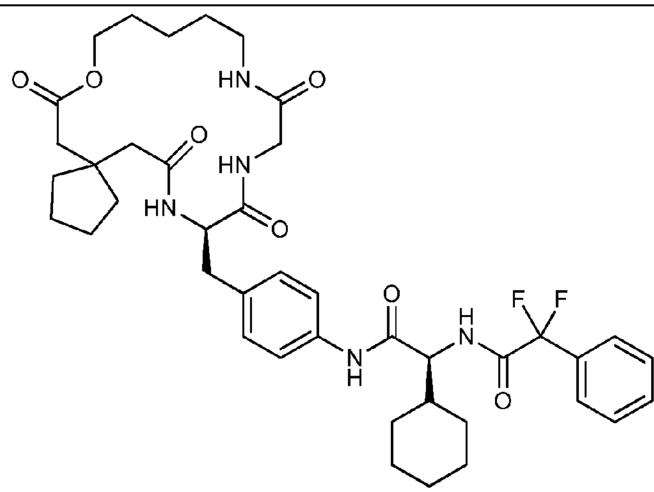
Compound No.	Structure
670	
671	

FIG. 12-268

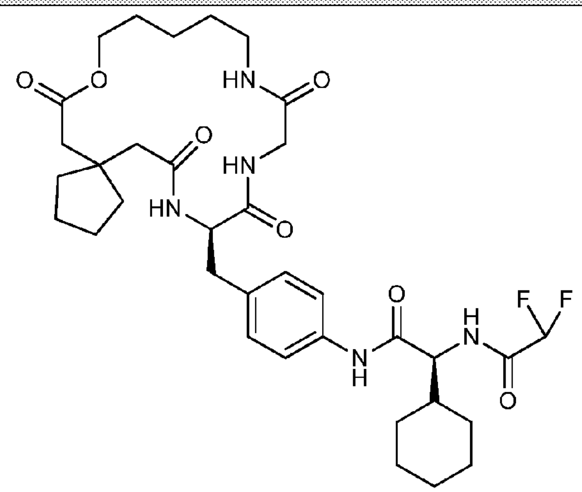
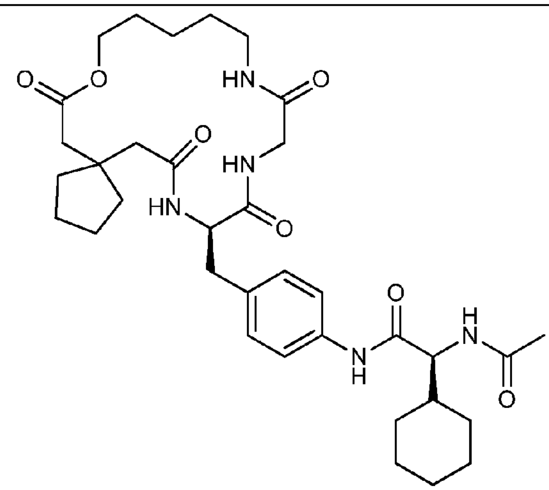
Compound No.	Structure
672	
673	

FIG. 12-269

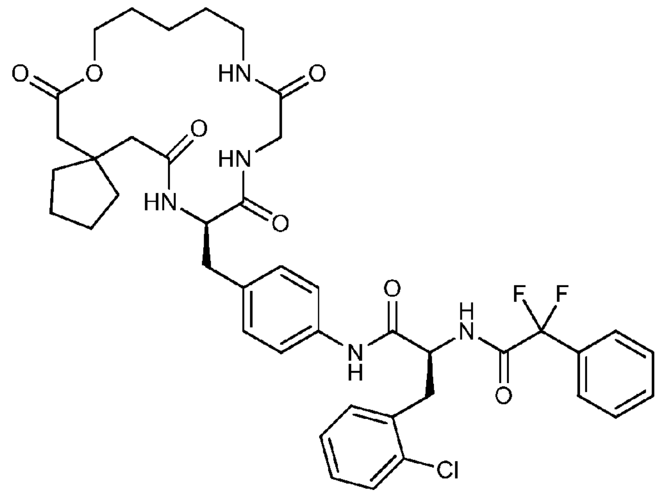
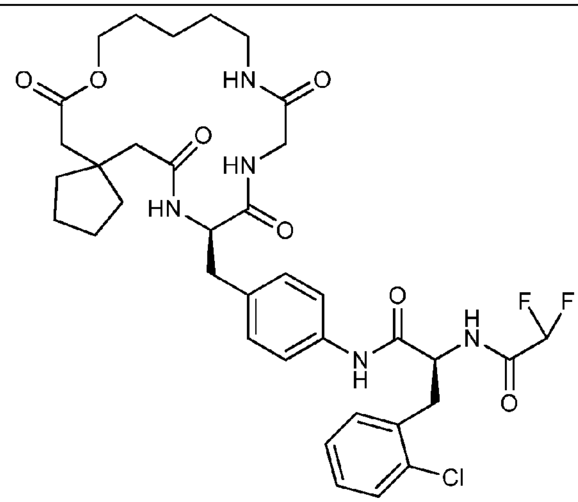
Compound No.	Structure
674	
675	

FIG. 12-270

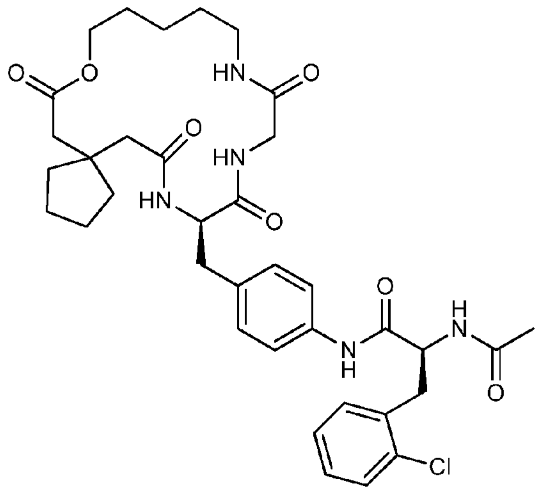
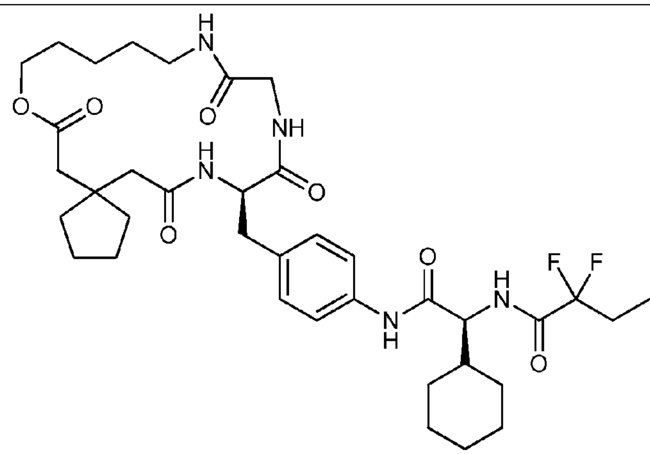
Compound No.	Structure
676	
677	

FIG. 12-271

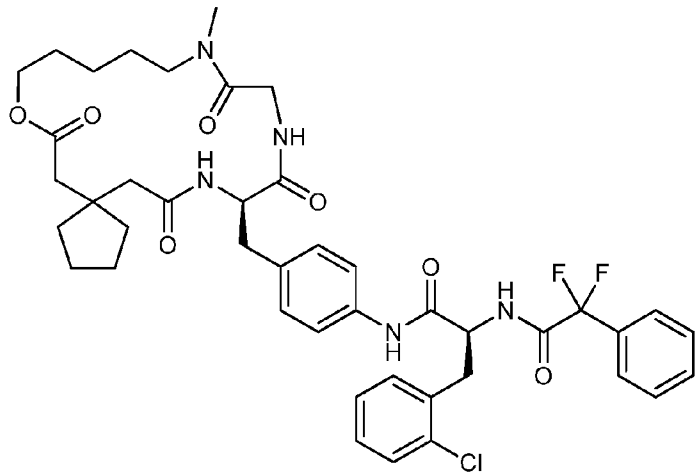
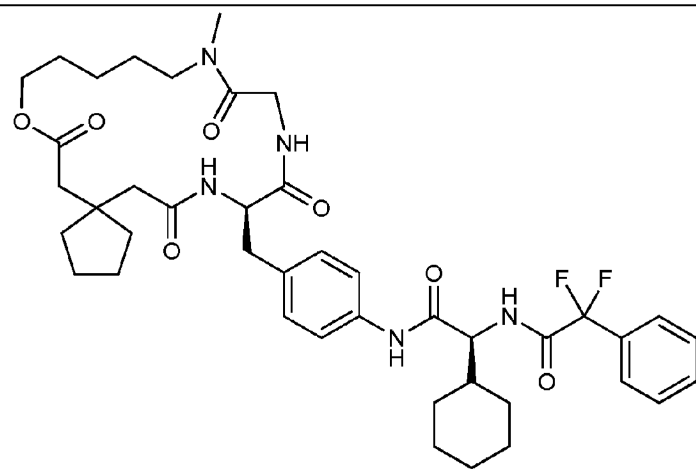
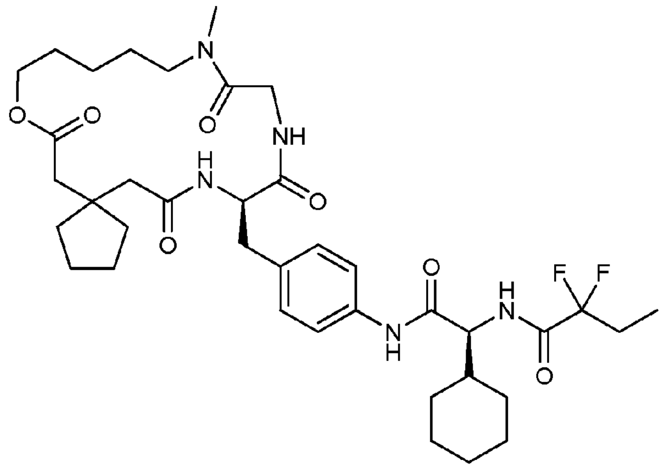
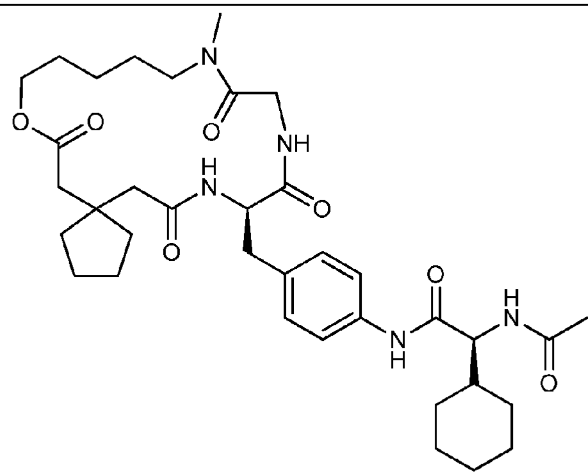
Compound No.	Structure
678	
679	

FIG. 12-272

Compound No.	Structure
680	
681	

MACROCYCLIC COMPOUNDS FOR MODULATING IL-17

CROSS REFERENCE TO RELATED APPLICATIONS

This application is the national stage of International (PCT) Patent Application serial number PCT/US2013/024386, filed Feb. 1, 2013, which claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 61/593,993, filed Feb. 2, 2012, and U.S. Provisional Patent Application Ser. No. 61/725,878, filed Nov. 13, 2012, the contents of each of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The invention relates generally to macrocyclic compounds and their therapeutic use. More particularly, the invention relates to macrocyclic compounds that modulate the activity of IL-17 and/or are useful in the treatment of medical conditions, such as inflammatory diseases and other IL-17-associated disorders.

BACKGROUND OF THE INVENTION

Interleukin-17 ("IL-17"), also known as IL-17A and CTLA-8, is a pro-inflammatory cytokine that stimulates secretion of various other cytokines in a variety of cell types. For example, IL-17 can induce IL-6, IL-8, G-CSF, TNF-α, IL-1β, PGE2, and IFN-γ, as well as numerous chemokines and other effectors. See, e.g., Gaffen, S L, Arthritis Research & Therapy 6: 240-247 (2004).

IL-17 is expressed by TH17 cells, which are involved in the pathology of inflammation and autoimmunity. It is also expressed by CD8+ T cells, γδ cells, NK cells, NKT cells, macrophages and dendritic cells. IL-17 and Th17 are linked to pathogenesis of diverse autoimmune and inflammatory diseases, but are essential to host defense against many microbes, particularly extracellular bacteria and fungi. Human IL-17A is a glycoprotein with a molecular weight of 17,000 daltons (Spriggs et al., J Clin Immunol, 17: 366-369 (1997)). IL-17 can form homodimers or heterodimers with its family member, IL-17F. IL-17 binds to both IL-17 RA and IL-17 RC to mediate signaling. IL-17, signaling through its receptor, activates the NF-κB transcription factor, as well as various MAPKs. See, e.g., Gaffen, S L, Nature Rev Immunol, 9: 556-567 (2009).

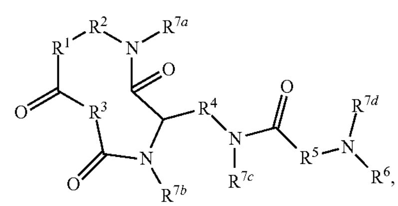
IL-17 can act in cooperation with other inflammatory cytokines such as TNF-α, IFN-γ, and IL-1β to mediate pro-inflammatory effects. See, e.g., Gaffen, S L, Arthritis Research & Therapy 6: 240-247 (2004). Increased levels of IL-17 have been implicated in numerous diseases, including rheumatoid arthritis (RA), bone erosion, intraperitoneal abscesses, inflammatory bowel disease, allograft rejection, psoriasis, angiogenesis, atherosclerosis, asthma, and multiple sclerosis. See, e.g., Gaffen, S L, Arthritis Research & Therapy 6: 240-247 (2004); US Publication No 20080269467 A1, published Oct. 30, 2008. IL-17 was found in higher serum concentrations in patients with systemic lupus erythematosus (SLE) and was recently determined to act either alone or in synergy with B-cell activating factor (BAFF) to control B-cell survival, proliferation, and differentiation into immunoglobulin producing cells. Doreau et al., Nature Immunology 7:778-785 (2009). IL-17 has also been associated with ocular surface disorders, such as dry eye (PCT publication WO2010062858 and WO2011163452). IL-17 has also been implicated in playing a role in ankylosing spondylitis (H. Appel et al., Arthritis Research and Therapy 2011, 13R95) and psoriatic arthritis (McInnes, I. et al. Arthritis & Rheumatism, 2011; Volume 63, Suppl. 10:779).

IL-17 and IL-17-producing TH17 cells have recently been implicated in certain cancers, Ji and Zhang, Cancer Immunol Immunother 59: 979-987 (2010). For example, IL-17-expressing TH17 cells were shown to be involved in multiple myeloma, Prabhala et al., Blood, online DOI 10.1182/blood-2009-10-246660, Apr. 15, 2010, and to correlate with poor prognosis in patients with hepatocellular carcinoma (HCC), Zhang et al., J Hepatology 50: 980-89 (2009). Also, IL-17 was found to be expressed by breast-cancer-associated macrophages, Zhu et al., Breast Cancer Research 10:R95 (2008). However, the role of IL-17 in cancer, in many cases, has been unclear. In particular, IL-17 and IL-17-producing TH17 cells have been identified as having both a positive and a negative role in tumor immunity, sometimes in the same type of cancer. For a review, see, Ji and Zhang, Cancer Immunol Immuother 59: 979-987 (2010).

It can be seen from above that modulation of IL-17 has important therapeutic implications. Although various antibodies to IL-17 have been described in the prior art, very few small molecule-type, specific modulators of IL-17 with oral bioavailability are known. Accordingly, there is a need for the development of small molecule-like modulators of IL-17.

SUMMARY

The present invention provides macrocyclic compounds, methods of modulating the activity of IL-17, and methods for treating various medical conditions using such compounds. In one aspect, the invention provides a compound represented by Formula I:



including pharmaceutically acceptable salts thereof, wherein the variables are as defined in the detailed description.

In another aspect, the invention provides a method of treating a patient suffering from or susceptible to a medical condition that is mediated directly or indirectly by IL-17. A number of medical conditions can be treated. The method comprises administering to the patient a therapeutically effective amount of a composition comprising a macrocyclic compound described herein. For example, the compounds described herein may be used to treat or prevent inflammatory diseases and conditions, proliferative diseases (e.g., cancer), autoimmune diseases and other disease described herein.

In another aspect, the invention provides a method of treating a patient suffering from a disease or condition associated with elevated levels of IL-17 comprising the steps of: a) determining whether the patient has an elevated level of IL-17; and b) if the patient does have an elevated level of IL-17, administering to the patient an effective amount of a compound of Formula I for a time sufficient to treat the disease or condition.

In still another aspect, the invention provides a method of treating a patient suffering from a disease or condition associated with elevated levels of IL-17 comprising the steps of: a) determining whether the patient has an elevated level of one or more IL-17-induced chemokine or effector; and b) if the patient does have an elevated level of the one or more IL-17 chemokine or effector, administering to the patient an effective amount of a compound of Formula I for a time sufficient to treat the disease or condition. In certain aspects, the IL-17 chemokine or effector is one or more of IL-6, IL-8, G-CSF, TNF-α, IL-1β, PGE2, and IFN-γ.

The foregoing and other aspects and embodiments of the invention may be more fully understood by reference to the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts the effect of two intraperitoneally dosed exemplary compounds of the invention (i.e., compound nos. 159 and 181) on edema, TNF-α, and IFN-γ in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and vehicle controls.

FIG. **2** depicts the dose-dependent effect of an intraperitoneally dosed exemplary compound of the invention (i.e., compound 159) on edema, IL-6, and IFN-γ in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and a vehicle control.

FIG. **3** depicts the dose-dependent effect of an orally dosed exemplary compound of the invention on edema, IL-6, and IFN-γ in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and a vehicle control.

FIG. **4** depicts the effect of an orally dosed exemplary compound of the invention on edema, IL-6, IFN-γ and CXCL-1 in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and various vehicle controls.

FIG. **5** depicts the dose-dependent effect of an orally dosed exemplary compound of the invention on edema, IL-6, and IFN-γ in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and various vehicle controls.

FIG. **6** depicts the effect over time on all paws of an orally dosed exemplary compound of the invention on Mean Clinical Arthritis Score in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and various vehicle controls.

FIG. **7** depicts the effect on all paws of an orally dosed exemplary compound of the invention on Clinical Arthritis Score in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and a vehicle control.

FIG. **8** depicts the effect on all joints of an orally dosed exemplary compound of the invention on various pathological parameters in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and a vehicle control.

FIG. **9** depicts the sum effect of an orally dosed exemplary compound of the invention on measured pathological parameters in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and a vehicle control.

FIG. **10** depicts the effect over time on all paws of two different dosages of an orally dosed exemplary compound of the invention on Mean Clinical Arthritis Score in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and vehicle controls.

FIG. **11** depicts the overall effect on all paws of two different dosages of an orally dosed exemplary compound of the invention on Mean Clinical Arthritis Score in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and vehicle controls.

FIG. **12** is a table of exemplary compounds of the invention (Table 1).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides macrocyclic compounds, methods of modulating the activity of IL-17, and methods for treating various medical conditions, especially inflammatory conditions and diseases, using such compounds. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, and biochemistry. For example, procedures for synthesizing organic compounds are described in the literature, such as "Comprehensive Organic Synthesis" (BM Trost & I Fleming, eds., 1991-1992). Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section. Further, when a variable is not accompanied by a definition, the previous definition of the variable controls.

I. DEFINITIONS

To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

The term "alkyl" is art-recognized and refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12} alkyl, C_1-C_{10} alkyl, and C_1-C_6 alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

The term "cycloalkyl" is art-recognized and refers to a monovalent fully saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl)hydrocarbon group of 3-10, 3-8, 4-8, or 4-6 carbons, referred to herein, e.g., as "C_{4-8} cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexane, cyclopentane, cyclobutane, and cyclopropane.

The term "alkylene" refers to the diradical of an alkyl group.

The term "C_0 alkylene" as used herein means a bond. Thus, a moiety defined herein as "—(C_0-C_6 alkylene)-aryl" includes both -aryl (i.e., C_0 alkylene-aryl) and —(C_1-C_6 alkylene)-aryl.

The terms "alkenylene" and "alkynylene" refer to the diradicals of an alkenyl and an alkynyl group, respectively.

The term "methylene unit" refers to a divalent —CH_2— group present in an alkyl or alkylene moiety.

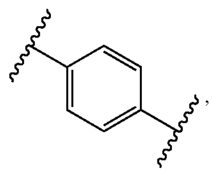
The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. For example, —CH_2F, —CHF_2, —CF_3, —CH_2CF_3, —CF_2CF_3, and the like.

The term "carbocyclyl", as used herein, means a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein each ring is either completely saturated or contains one or more units of unsaturation, but where no ring is aromatic. Representative carbocyclyl groups include cycloalkyl groups (e.g., cyclopentyl, cyclobutyl, cyclopentyl, cyclohexyl and the like), and cycloalkenyl groups (e.g., cyclopentenyl, cyclohexenyl, cyclopentadienyl, and the like).

The term “aryl” is art-recognized and refers to a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein at least one ring is aromatic. Representative aryl groups include fully aromatic ring systems, such as phenyl, naphthyl, and anthracenyl, and ring systems where an aromatic carbon ring is fused to one or more non-aromatic carbon rings, such as indanyl, phthalimidyl, naphthimidyl, or tetrahydronaphthyl, and the like.

The term “arylene” refers to the diradical of an aryl group.

The term “1,4-phenylene” refers to a diradical of phenyl having the formula:



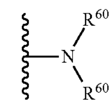
wherein each “∿” represents a connection to the rest of the compound.

The term “heteroaryl” is art-recognized and refers to monocyclic, bicyclic or polycyclic ring system wherein at least one ring is both aromatic and comprises a heteroatom; and wherein no other rings are heterocyclyl (as defined below). In certain instances, a ring which is aromatic and comprises a heteroatom contains 1, 2, 3, or 4 ring heteroatoms in such ring. Representative heteroaryl groups include ring systems where (i) each ring comprises a heteroatom and is aromatic, e.g., imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrrolyl, furanyl, thiophenyl pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl; (ii) each ring is aromatic or carbocyclyl, at least one aromatic ring comprises a heteroatom and at least one other ring is a hydrocarbon ring or e.g., indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, pyrido[2,3-b]-1,4-oxazin-3(4H)-one, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl; and (iii) each ring is aromatic or carbocyclyl, and at least one aromatic ring shares a bridgehead heteroatom with another aromatic ring, e.g., 4H-quinolizinyl.

The term “heterocyclyl” refers to monocyclic, bicyclic and polycyclic ring systems where at least one ring is saturated or partially unsaturated (but not aromatic) and comprises a heteroatom. A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Representative heterocyclyls include ring systems in which (i) every ring is non-aromatic and at least one ring comprises a heteroatom, e.g., tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl; (ii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is an aromatic carbon ring, e.g., 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl; and (iii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is aromatic and comprises a heteroatom, e.g., 3,4-dihydro-1H-pyrano[4,3-c]pyridine, and 1,2,3,4-tetrahydro-2,6-naphthyridine.

The term “saturated heterocyclyl” refers to a heterocyclyl wherein every ring is saturated, e.g., tetrahydrofuran, tetrahydro-2H-pyran, pyrrolidine, piperidine and piperazine.

The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formula:



wherein each R^{60} independently represent hydrogen or alkyl.

The terms “alkoxyl” or “alkoxy” are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An “ether” is two hydrocarbons covalently linked by an oxygen. The term “alkenyloxy” is art-recognized and refers to an alkenyl group, as defined above, having an oxygen radical attached thereto.

In general, the term “substituted”, whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. Combinations of substituents envisioned under this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group (such as an alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene or the carbon atom of a carbocyclyl, aryl, heterocyclyl or heteroaryl) are independently halogen; $—(CH_2)_{0-4}R^\circ$; $—(CH_2)_{0-4}OR^\circ$; $—O—(CH_2)_{0-4}C(O)OR^\circ$; $—(CH_2)_{0-4}—CH(OR^\circ)_2$; $—(CH_2)_{0-4}SR^\circ$; $—(CH_2)_{0-4}Ph$, which may be substituted with R°; $—(CH_2)_{0-4}O(CH_2)_{0-4}Ph$ which may be substituted with R°; $—CH{=}CHPh$, which may be substituted with R°; $—NO_2$; $—CN$; $—N_3$; $—(CH_2)_{0-4}N(R^\circ)_2$; $—(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $—N(R^\circ C(S)R^\circ$; $—(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $—N(R^\circ)C(S)NR^\circ_2$; $—(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $—N(R^\circ)N(R^\circ C(O)R^\circ$; $—N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $—N(R^\circ)N(R^\circ C(O)OR^\circ$; $—(CH_2)_{0-4}C(O)R^\circ$; $—C(S)R^\circ$; $—(CH_2)_{0-4}C(O)OR^\circ$; $—(CH_2)_{0-4}C(O)SR^\circ$; $—(CH_2)_{0-4}C(O)OSiR^\circ_3$; $—(CH_2)_{0-4}OC(O)R^\circ$; $—OC(O)(CH_2)_{0-4}SR^\circ—$, $SC(S)SR^\circ$; $—(CH_2)_{0-4}SC(O)R^\circ$; $—(CH_2)_{0-4}C(O)NR^\circ_2$; $—C(S)NR^\circ_2$; $—C(S)SR^\circ$; $—(CH_2)_{0-4}OC(O)NR^\circ_2$; $—C(O)N(OR^\circ)R^\circ$; $—C(O)C(O)R^\circ$; $—C(O)CH_2C(O)R^\circ$; $—C(NOR^\circ)\ R^\circ$; $—(CH_2)_{0-4}SSR^\circ$; $—(CH_2)_{0-4}S(O)_2R^\circ$; $—(CH_2)_{0-4}S(O)_2OR^\circ$; $—(CH_2)_{0-4}OS(O)_2R^\circ$; $—S(O)_2NR^\circ_2$; $—(CH_2)_{0-4}S(O)R^\circ$; $—N(R^\circ)S(O)_2NR^\circ_2$; $—N(R^\circ)S(O)_2R^\circ$; $—N(OR^\circ)R^\circ$; $—C(NH)NR^\circ_2$; $—P(O)_2R^\circ$; $—P(O)RO_2$; $—OP(O)RO_2$; $—OP(O)(OR^\circ)_2$; $—SiR^\circ_3$; $—(C_{1-4}$ straight or branched) alkylene)-$N(R^\circ)_2$; or $—(C_{1-4}$ straight or branched) alkylene)

$C(O)O—N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $—CH_2Ph$, $—O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $—(CH_2)_{0-2}R^\bullet$, -(halo$R^\bullet$), $—(CH_2)_{0-2}OH$, $—(CH_2)_{0-2}OR^\bullet$, $—(CH_2)_{0-2}CH(OR^\bullet)_2$; —O(halo$R^\bullet$), —CN, $—N_3$, $—(CH_2)_{0-2}C(O)R^\bullet$, $—(CH_2)_{0-2}C(O)OH$, $—(CH_2)_{0-2}C(O)OR^\bullet$, $—(CH_2)_{0-2}SR^\bullet$, $—(CH_2)_{0-2}SH$, $—(CH_2)_{0-2}NH_2$, $—(CH_2)_{0-2}NHR^\bullet$, $—(CH_2)_{0-2}NR^\bullet_2$, $—NO_2$, $—SiR^\bullet_3$, $—OSiR^\bullet_3$, $—C(O)SR^\bullet$, —(C_{1-4} straight or branched alkylene)$C(O)OR^\bullet$, or $—SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $—CH_2Ph$, $—O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include ═O and ═S.

Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: ═O, ═S, $═NNR^*_2$, $═NNHC(O)R^*$, $═NNHC(O)OR^*$, $═NNHS(O)_2R^*$, $═NR^*$, $═NOR^*$, $—O(C(R^*_2))_{2-3}O—$, or $—S(C(R^*_2))_{2-3}S—$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $—O(C(R^*)_2)_{2-3}O—$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of R^* include halogen, $—R^\bullet$, -(halo$R^\bullet$), —OH, $—OR^\bullet$, —O(halo$R^\bullet$), —CN, —C(O)OH, $—C(O)OR^\bullet$, $—NH_2$, $—NHR^\bullet$, $—NR^\bullet_2$, or $—NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $—CH_2Ph$, $—O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $—R^\dagger$, $—NR^\dagger_2$, $—C(O)R^\dagger$, $—C(O)OR^\dagger$, $—C(O)C(O)R^\dagger$, $—C(O)CH_2C(O)R^\dagger$, $—S(O)_2R^\dagger$, $—S(O)_2NR^\dagger_2$, $—C(S)NR^\dagger_2$, $—C(NH)NR^\dagger_2$, or $—N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted —OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of Rt are independently halogen, $—R^\bullet$, -(halo$R^\bullet$), —OH, $—OR^\bullet$, —O(halo$R^\bullet$), —CN, —C(O)OH, $—C(O)OR^\bullet$, $—NH_2$, $—NHR^\bullet$, $—NR^\bullet_2$, or $—NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4}aliphatic, $—CH_2Ph$, $—O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

The term "moiety" refers to a portion of a compound of this invention comprising at least one hydrogen atom and at least one carbon atom.

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivatizing with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound, as well as enantiomeric mixtures thereof.

As used herein, the term "patient" refers to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (e.g., murines, simians, equines, bovines, porcines, canines, felines, and the like), and most preferably includes humans.

As used herein, the term "effective amount" refers to the amount of a compound (e.g., a compound of the present invention) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, e.g., lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use in vivo or ex vivo.

As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (e.g., acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

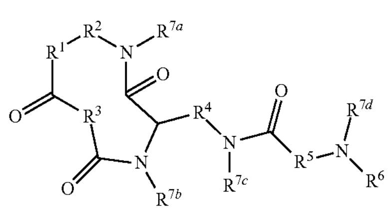
Examples of bases include, but are not limited to, alkali metals (e.g., sodium) hydroxides, alkaline earth metals (e.g., magnesium) hydroxides, ammonia, and compounds of formula NW_4^+ hydroxide, wherein W is C_{1-4} alkyl, and the like.

Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like.

For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

II. MACROCYCLIC COMPOUNDS

In one aspect, the invention provides a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from —O— and —N((C_0-C_3 alkylene)-Q)-, wherein

Q is selected from hydrogen, —N(R^{2e}), —OH, —O—C_1-C_4 alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

the alkylene portion of R^1, if present, is optionally substituted; and

when the —C(O)— group adjacent to R^1 is bound directly to an —N(R^{2h})— in R^3, R^1 is additionally selected from —CH_2—;

R^2 is an optionally substituted C_3-C_{12} alkylene, optionally substituted C_3-C_{12} alkenylene, or optionally substituted C_3-C_{12} alkynylene, wherein:

up to three methylene units of R^2 are optionally and independently replaced with —O—, —N(R^c)—, —S—, —S(O)—, or —S(O)$_2$—, wherein

R^c is selected from hydrogen, C_1-C_4 alkyl, —C(O)—C_1-C_3 alkyl, —C(O)—(C_1-C_3 alkylene)-aryl, —C(O)—(C_1-C_3 alkylene)-heteroaryl, —C(O)—O—C_1-C_3 alkyl, —C(O)—O—C_1-C_3 alkenyl, —S(O)$_2$—C_1-C_3 alkyl, —S(O)$_2$—(C_1-C_3 alkylene)-aryl, and —S(O)$_2$—(C_1-C_3 alkylene)-heteroaryl; or

when R^1 is —N((C_0-C_3 alkylene)-Q)-, R^c is optionally taken together with R^1 and any intervening atoms to form a heterocyclyl;

any two substituents bound to a common carbon atom in R^2 are optionally taken together to form ═O, carbocyclyl, or heterocyclyl;

any two substituents bound to different carbon atoms in R^2 are optionally taken together with any intervening atoms to form an aryl, heteroaryl, carbocyclyl, or heterocyclyl;

any two R^c are optionally taken together with the nitrogen atoms to which they are bound and any intervening atoms to form a heterocyclyl; and

any substituent bound to a carbon atom in R^2 is optionally taken together with any one R^c or with R^{7a} and any intervening atoms to form heteroaryl or heterocyclyl;

R^3 is —[C(R^d)(R^d)]$_p$-[N(R^{7h})]$_{0\text{-}1}$—[C(R^d)(R^d)]$_q$—, wherein:

each R^d is independently selected from hydrogen and a suitable alkylene substituent; and any two R^d are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl, or heterocyclyl;

p is 0, 1 or 2;

q is 0, 1 or 2; and

p+q is 2 or more;

R^4 is —[C(R^e)(R^e)]$_n$—Y—[C(R^e)(R^e)]$_m$—, wherein:

each R^e is independently selected from hydrogen and a suitable alkylene substituent;

Y is selected from aryl, heteroaryl, carbocyclyl, heterocyclyl, and optionally substituted C_1-C_3 alkylene;

each of n and m are independently selected from 0, 1, 2, 3, 4, 5, and 6; and n+m is 6 or less;

R^5 is C_1-C_2 alkylene substituted with one or more —(C_0-C_5 alkylene)-R^f, wherein each R^f is independently selected from —CH_3, —O—C_1-C_3 alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R^6 is selected from heteroaryl, —CH_2-aryl, —C(O)—R^8, —C(O)—O—R^8, —C(O)—C(O)—R^8, —S(O)—R^8, —S(O)$_2$—R^8, C(O)—N(R^{2f})—R^8, and —S(O)$_2$—N(R^{2f})—R^8;

each R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} is independently selected from hydrogen and C_1-C_4 alkyl;

R^{7h} is independently selected from hydrogen, C_1-C_4 alkyl, phenyl, and benzyl;

R^8 is selected from —(C_0-C_6 alkylene)-aryl, —(C_0-C_6 alkylene)-heteroaryl, —(C_0-C_6 alkylene)-carbocyclyl, —(C_0-C_6 alkylene)-heterocyclyl, and C_1-C_6 alkyl, wherein

when R^8 is C_1-C_6 alkyl, up to two methylene units in the alkyl are optionally and independently replaced with —O—, —N(R^{7g})—, —S—, —S(O)—, or —S(O)$_2$—; and

any alkyl or alkylene portion of R^8 is optionally substituted with an appropriate alkyl or alkylene substituent other than ═O; or

R^{7d} and R^6 are optionally taken together to form a heterocyclyl; and

any aryl, heteroaryl, carbocyclyl, or heterocyclyl portion of the compound is optionally substituted.

It will be understood by those of skill in the art that the optional and independent replacement of up to three methylene units of R^2 with —O—, —$N(R^c)$—, —S—, —S(O)—, or —$S(O)_2$—, contemplated by the present invention only includes such replacements that result in a stable compound. Accordingly, compounds containing combinations of such replacements that are known to be unstable, e.g., —O—O—, —S(O)—$S(O)_2$—, —$N(R^c)$—$N(R^c)$—O—, and the like, are not to be considered within the scope of the invention. It will be understood by those of skill in the art that because the compounds of the invention are limited to compounds that are stable, compounds formed by the optional and independent replacement of up to three methylene units in R^2 with certain combinations of —O—, —S—, —S(O)—, —$S(O)_2$—, or —NR^c— are not within the scope of the present invention. For example, compounds wherein the R^2 moiety comprises an —O—, —S—, —S(O)—, —$S(O)_2$, or —$N(R^c)$—, adjacent to an —O—, —S—, —S(O)—, —$S(O)_2$, or —$N(R^c)$— are not within the scope of the present invention, except for an —$S(O)_2$— adjacent a —$N(R^c)$—. In addition, R^2 should not comprise —O—CH_2—O—, —N—CH_2—O—, or —O—CH_2—N—, wherein the —CH_2— portion thereof is optionally substituted, except when the —CH_2— portion is substituted to become —C(O)—.

In certain embodiments of Formula I, R^1 is selected from —O— and —N((C_0-C_3 alkylene)-Q)-, wherein Q is selected from hydrogen, —$N(R^{7e})$, —OH, —O—C_1-C_4 alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl.

In certain embodiments of Formula I, R^1 is selected from —O—, —NH— and —N(C_1-C_3 alkyl-OH)—. In one aspect of these embodiments, R^1 is selected from —O—, —NH— and —$N(CH_2CH_2OH)$—.

In other embodiments of Formula I, R^1 is selected from —O—, —NH— and —$N(CH_3)$—.

In still other embodiments of Formula I, when the —C(O)— group adjacent to R^1 is bound directly to an —$N(R^{7h})$— in R^3, R^1 is —CH_2—

In certain embodiments of Formula I, R^2 is an optionally substituted C_5-C_{12} alkylene, optionally substituted C_5-C_{12} alkenylene, or optionally substituted C_5-C_{12} alkynylene, wherein:

- up to three methylene units of R^2 are optionally and independently replaced with —O—, —$N(R^c)$—, —S—, —S(O)—, or —$S(O)_2$—, wherein R^c is selected from hydrogen, C_1-C_4 alkyl, C(O)—C_1-C_3 alkyl, C(O)—(C_1-C_3 alkylene)-aryl, C(O)—(C_1-C_3 alkylene)-heteroaryl, $S(O)_2$—C_1-C_3 alkyl, $S(O)_2$—(C_1-C_3 alkylene)-aryl, and $S(O)_2$—(C_1-C_3 alkylene)-heteroaryl;
- any two substituents bound to a common carbon atom in R^2 are optionally taken together to form =O, carbocyclyl or heterocyclyl;
- any two substituents bound to different carbon atoms in R^2 are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl;
- any substituent bound to a carbon atom in R^2 and any one R^c are optionally taken together with any intervening atoms to form heteroaryl or heterocyclyl; and
- any substituent bound to two R^c are optionally taken together with any intervening atoms to form a heterocyclyl.

In certain embodiments of Formula I, R^2 is selected from *—$CH(R^{10})$—$(CH_2)_{2-4}$—NH—C(O)—$(C(R^{11})_2)_{1-5}$—, *—$CH(R^{10})$—$(CH_2)_{4-8}$—, *—$CH(R^{10})$—$(CH_2)_{2-4}$-(1,4-phenylene)-NH—C(O)—$(C(R^{11})_2)_{1-3}$—, and *—$CH(R^{10})$—$(CH_2)_{2-4}$-(1,4-phenylene)-; R^{10} is selected from hydrogen, —C(O)—O—C_1-C_4 alkyl, and —C(O)—OH; and each R^{11} is independently selected from hydrogen, benzyl, C_1-C_4 alkyl and C_1-C_4 hydroxyalkyl, wherein no more than two R^{11} are other than hydrogen; one methylene unit in a specified —$(CH_2)_{2-4}$ or —$(CH_2)_{4-8}$ portion of R^2 is optionally replaced with —N(H)— or —$N(CH_3)$—; and "*" represents a terminus of R^2 bound to R^1. In one aspect of these embodiments, R^2 is selected from *—$CH(R^{10})$—$(CH_2)_{2-4}$—NH—C(O)—$(CH_2)_{1-5}$—, *—$CH(R^{10})$—$(CH_2)_4$—, *—$CH(R^{10})$—$(CH_2)_{2-4}$—NH—C(O)—$C((CH_3)_2)$—, *—$CH(R^{10})$—$(CH_2)_{2-4}$ —NH—C(O)—$CH(CH_2OH)$—, *—$CH(R^{10})$—CH_2-(1,4-phenylene)-NH—C(O)—$(CH_2)_{1-3}$—, *—$CH(R^{10})$—CH_2-(1,4-phenylene)-, —$(CH_2)_8$—, *—$(CH_2)_2$—$N(CH_3)$—$(CH_2)_2$—NH—C(O)—CH_2—, and *—$(CH_2)_5$—NH—C(O)—CH(benzyl)-; and R^{10} is selected from hydrogen, —C(O)—O—CH_3, and C(O)—OH.

The term "specified —$(CH_2)_{2-4}$— or —$(CH_2)_{4-8}$— portion of R^2" as used in the preceding paragraph refers to those embodiments of R^2 comprising portions that are indicated as —$(CH_2)_{2-4}$— or —$(CH_2)_{4-8}$—. For example, when R^2 is —$CH(R^{10})$—$(CH_2)_{2-4}$—NH—C(O)—$(CH_2)_{1-5}$—, only the bolded portion is a "specified —$(CH_2)_{2-4}$— portion of R^2."

In other embodiments of Formula I, R^2 is selected from *—$CH(R^{10})$—Z—, or *—$CH(R^{10})$—X—$CH(R^{10})$—$N(R^{12})$—C(O)—$CH(R^{11})$—$(CH_2)_{0-2}$—, wherein:

X is selected from —CH_2—O—CH_2—, —CH_2—$N(R^{13})$—CH_2—, —CH_2—N(H)—C(O)—, —CH_2—, —$(CH_2)_2$—, and —$(CH_2)_3$—;

Z is selected from C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene, wherein up to 2 methylene units in Z are optionally and independently replaced with —O—, —NH— or —$N(CH_3)$—;

each R^{10} is independently selected from hydrogen, —C(O)OH, and —$C(O)OCH_3$, wherein at least one R^{10} is hydrogen;

R^{11} is selected from hydrogen, (S)—CH_2OH, (S)—CH_3, (S)—$C(CH_3)_3$, (S)-benzyl, (R)-benzyl, (S)—CH_2-pyridinyl, (S)-cyclohexyl, (S)—CH_2-cyclohexyl, (S)—$(CH_2)_2$—COOH, (S)—$(CH_2)_2$—$C(O)NH_2$, and (S)—$(CH_2)_4$—NH_2;

R^{12} is selected from hydrogen and —CH_3;

R^{13} is selected from hydrogen and —CH_3; or

R^{13} is optionally taken together with R^{12} or the —N((C_0-C_3 alkylene)-Q) portion of R^1 to form a heterocyclyl.

In certain embodiments of Formula I, Z is selected from *—$(CH_2)_{3-9}$—, *—CH(COOH)—$(CH_2)_{2-8}$—, *—$(CH_2)_2$—O—$(CH_2)_2$—, *—$(CH_2)_2$—O—$(CH_2)_2$—O—$(CH_2)_2$—, *—$(CH_2)_2$—NH—$(CH_2)_2$—, *—$(CH_2)_2$—$N(CH_3)$—$(CH_2)_2$—, *—CH_2—C≡C—$(CH_2)_{4-5}$, and *—CH_2—CH=CH—$(CH_2)_{4-5}$.

In other embodiments of Formula I, R^2 is selected from *—$(CH_2)_{3-9}$—, *—CH(COOH)—$(CH_2)_{2-8}$—, *—$(CH_2)_2$—O—$(CH_2)_2$—, *—$(CH_2)_2$—O—$(CH_2)_2$—O—$(CH_2)_2$—, *—$(CH_2)_2$—NH—$(CH_2)_2$—, *—$(CH_2)_2$—$N(CH_3)$—$(CH_2)_2$—, *—CH_2—C≡C—$(CH_2)_{4-5}$, and *—CH_2—CH=CH—$(CH_2)_{4-5}$.

In other embodiments of Formula I, R^2 is selected from)*—$CH(R^{10}$—Z— and *—$C(H)(R^{10})$—X—$C(H)(R^{10})$—$N(R^{12})$—C(O)—$C(H)(R^{11})$—$(CH_2)_{0-2}$—, wherein:

X is selected from —CH_2—O—CH_2—, —CH_2—N(H)—CH_2—, —CH_2—$N(CH_3)$—CH_2—, —CH_2—, —$(CH_2)_2$—, and —$(CH_2)_3$—;

Z is selected from C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene, wherein up to 2 methylene units in Z are optionally and independently replaced with —O—, —N(H)— or —$N(CH_3)$—;

each R^{10} is independently selected from hydrogen and —(R)—COOH, wherein at least one R^{10} is hydrogen;

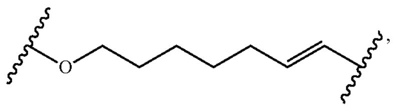
R^{11} is selected from hydrogen, (S)—CH_2OH, (S)—CH_3, (S)—$C(CH_3)_3$, (S)-benzyl, (R)-benzyl, (S)—CH_2-pyridinyl, (S)-cyclohexyl, (S)—CH_2-cyclohexyl, (S)—$(CH_2)_2$—COOH, (S)—$(CH_2)_2$—$C(O)NH_2$, and (S)—$(CH_2)_4$—NH_2;

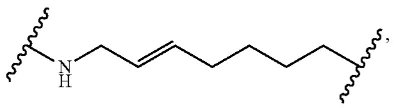
R^{12} is selected from hydrogen and —CH_3; and

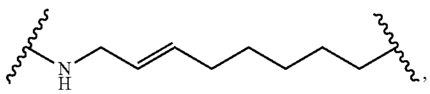
"*" represents a terminus of R^2 bound to R^1.

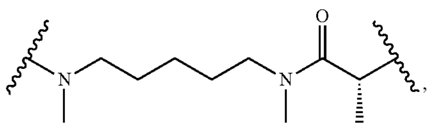
In certain embodiments, p+q is 2, 3, or 4. In other embodiments, p+q is 3.

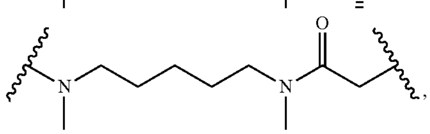
In a more specific embodiment, the portion of the compound represented by —R^1-R^2 is selected from:

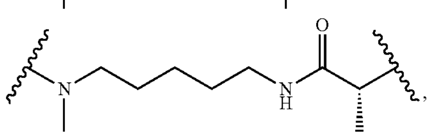


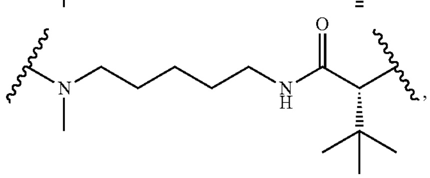


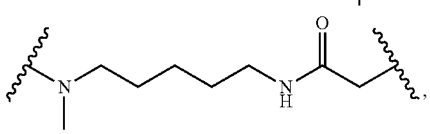


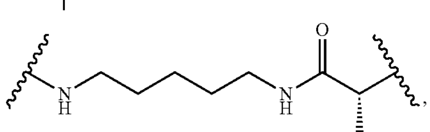


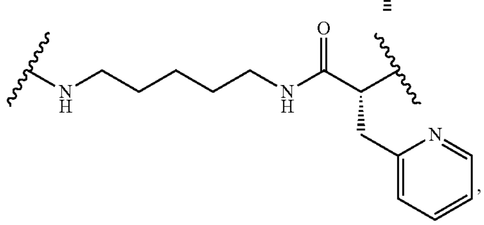


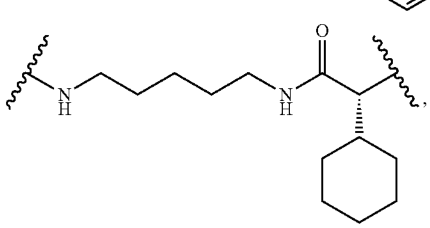




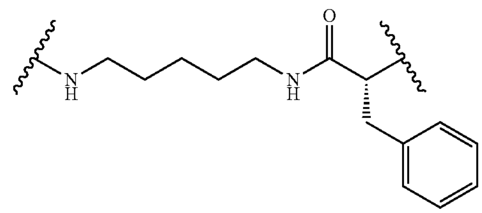


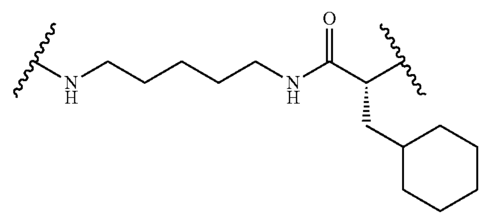


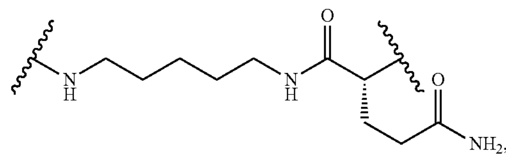


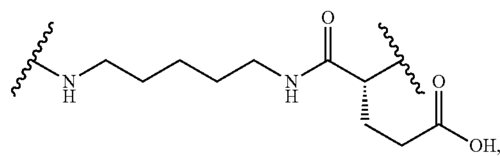


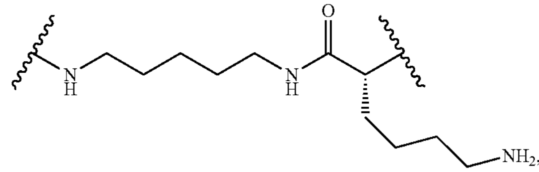
-continued

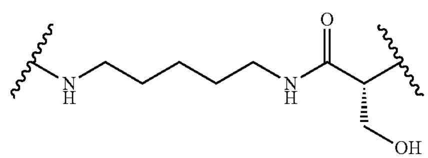


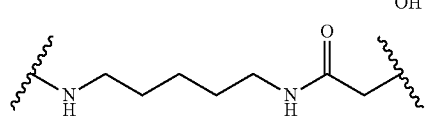


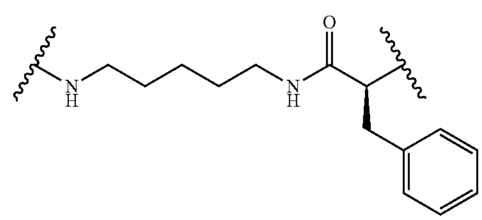


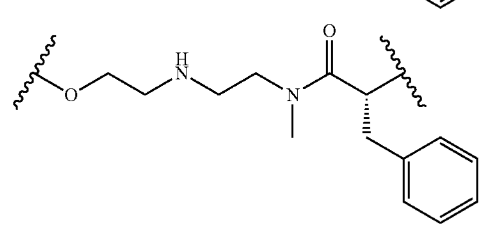




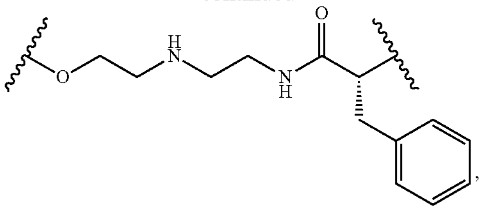


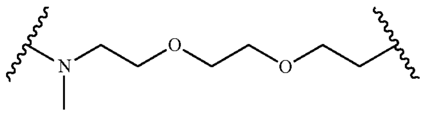


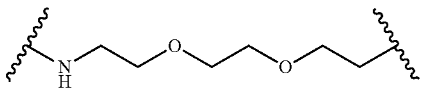


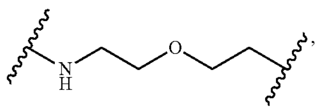


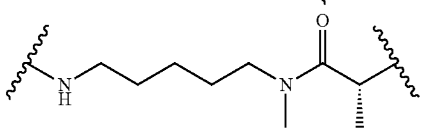
-continued

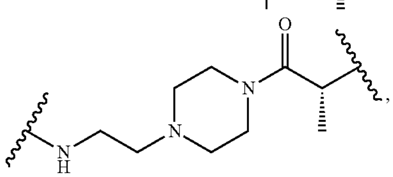


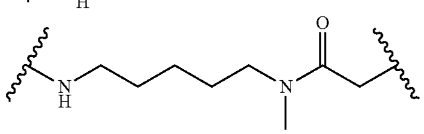


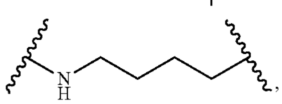


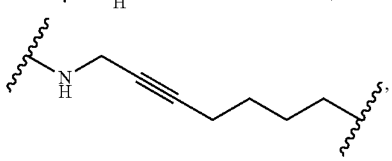


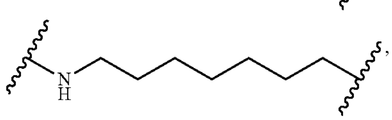


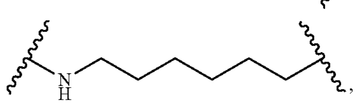


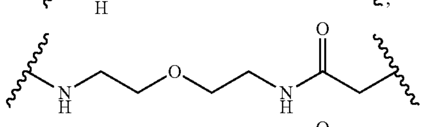


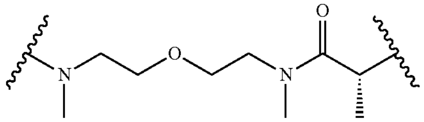


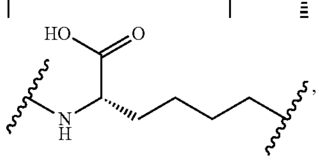




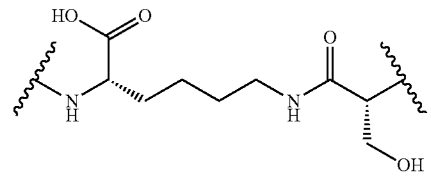


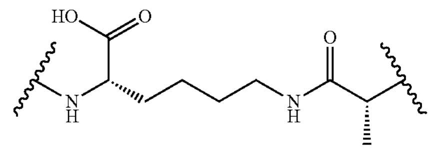


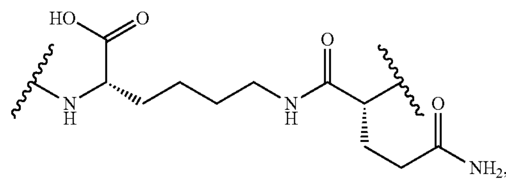


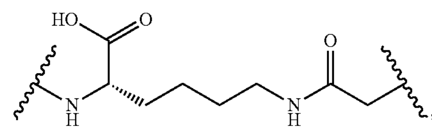


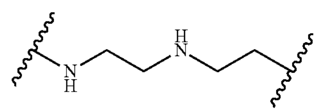
-continued

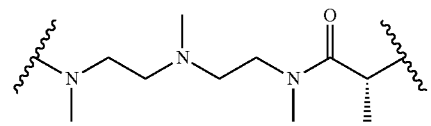


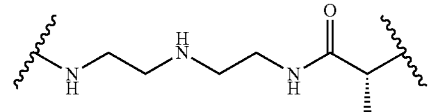


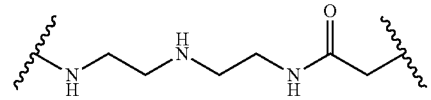


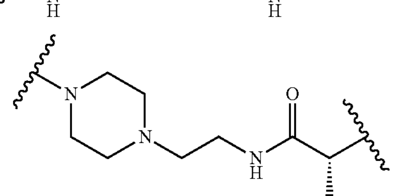


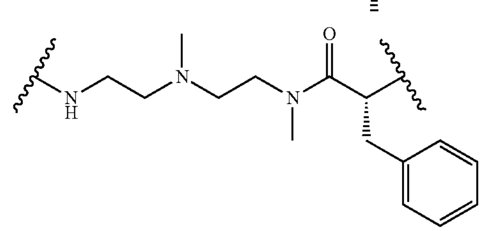


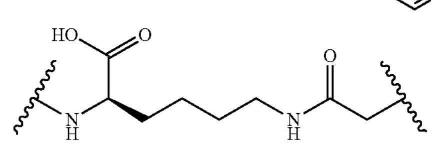




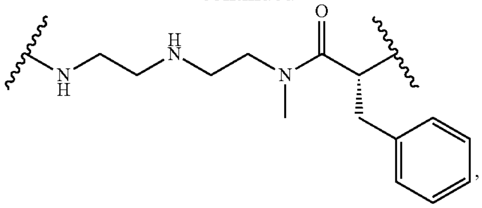


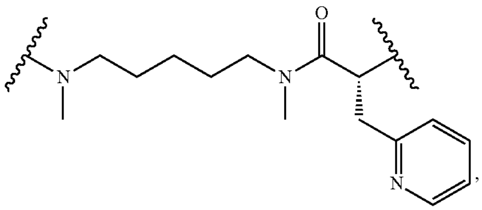


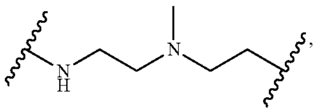


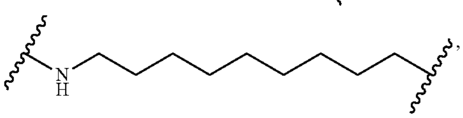


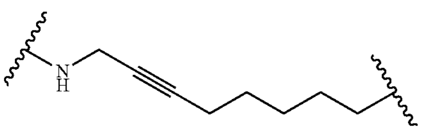
-continued

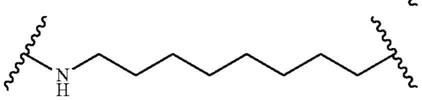


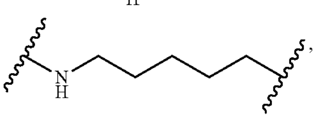


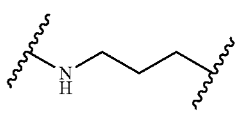


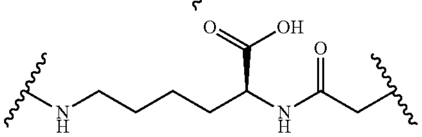


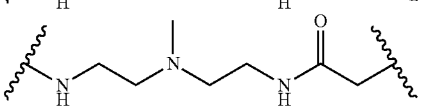


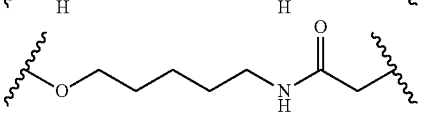


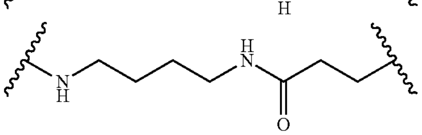


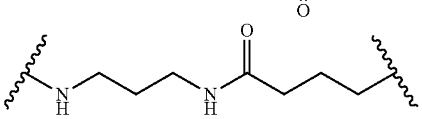




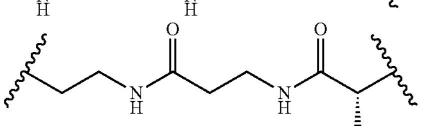




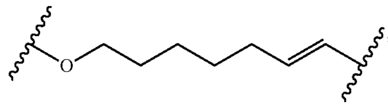


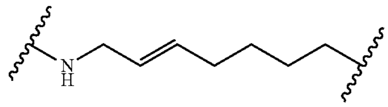


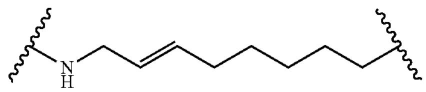
and

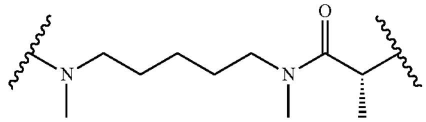


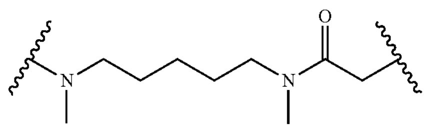
In certain other embodiments, the portion of the compound represented by —R^1-R^2 is selected from:

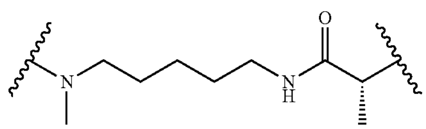


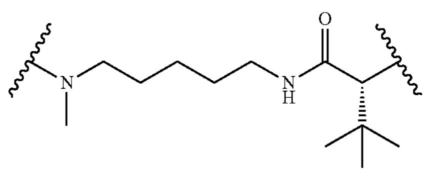


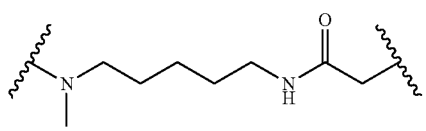


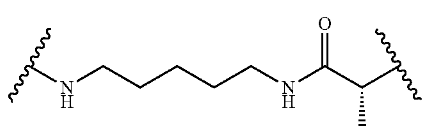


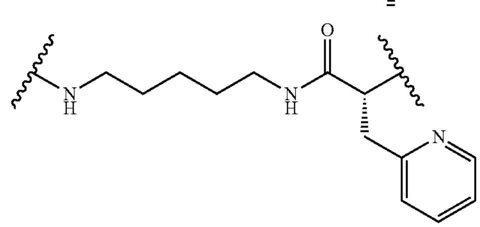


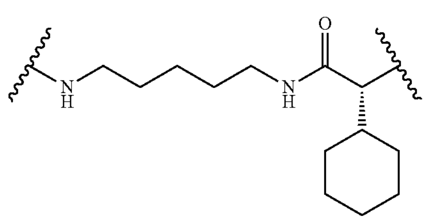




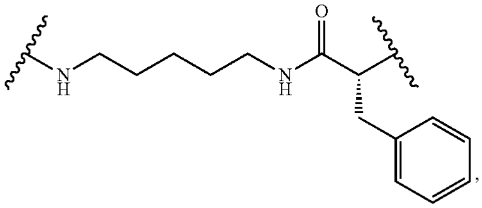


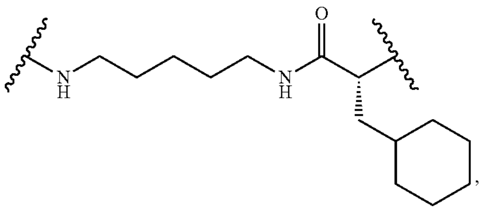


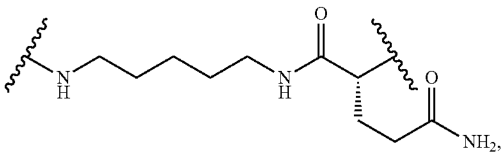


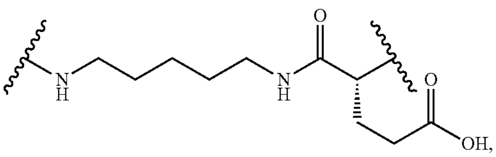


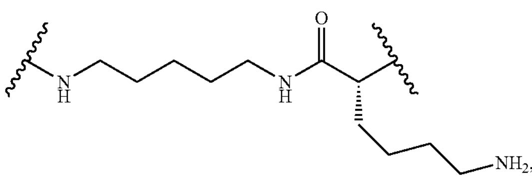
-continued

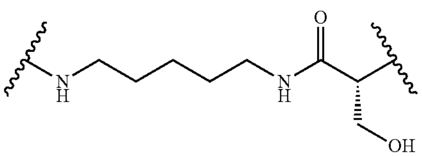


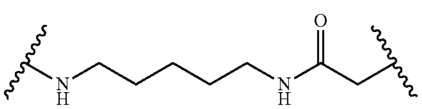


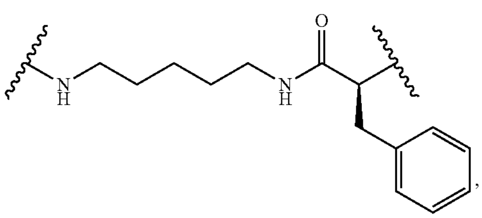


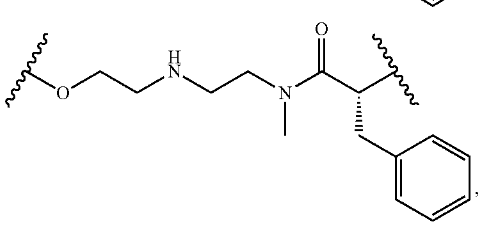




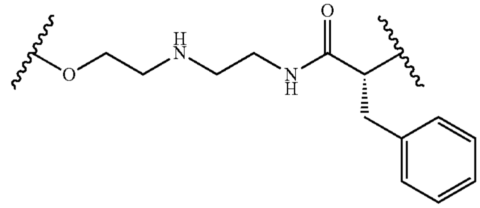


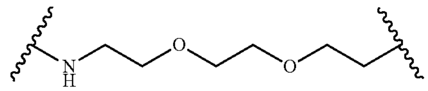


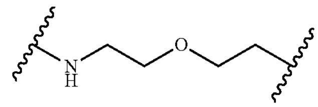


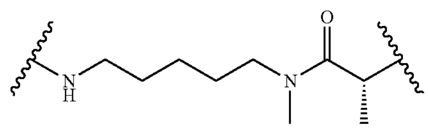


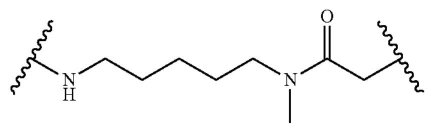
-continued

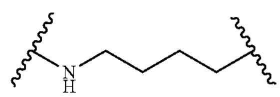


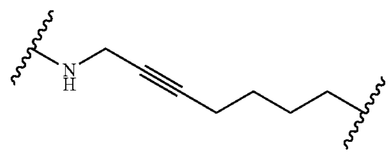


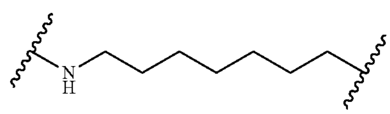


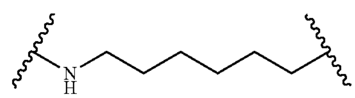


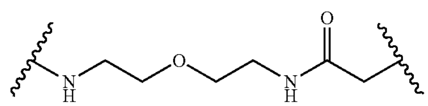


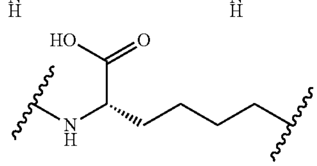


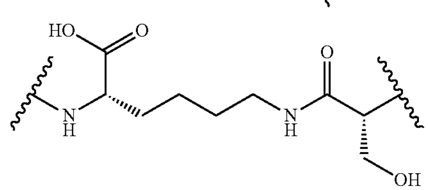


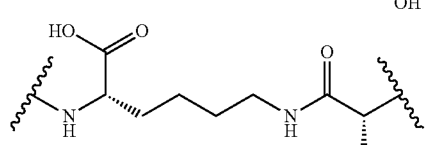




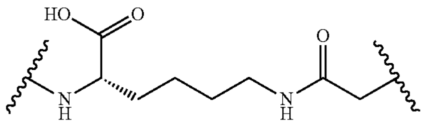


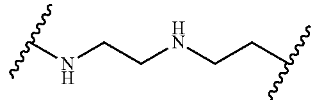


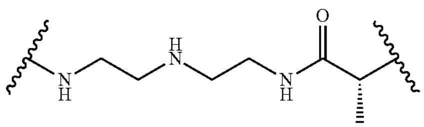


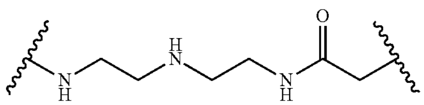


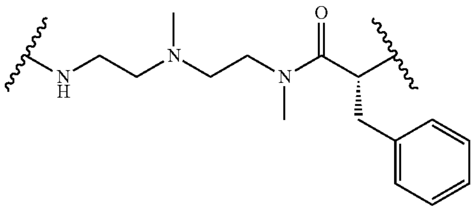
-continued

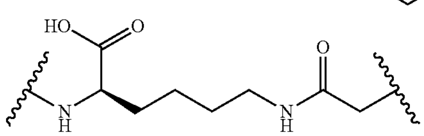


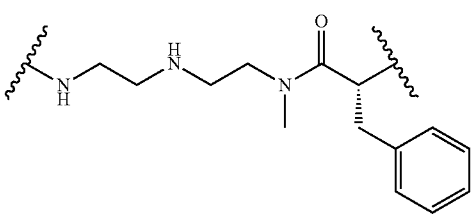


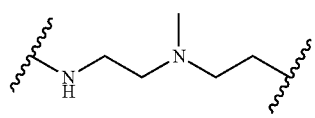


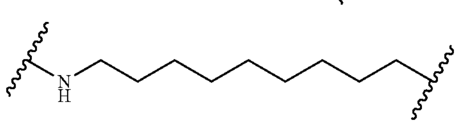


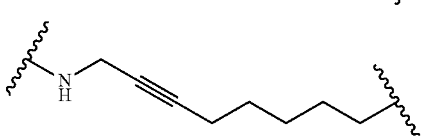


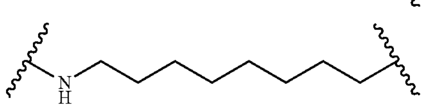


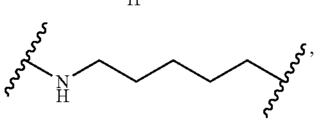


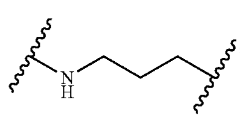


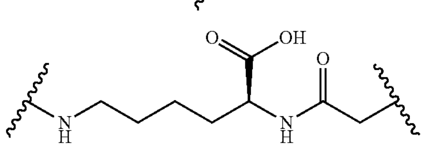




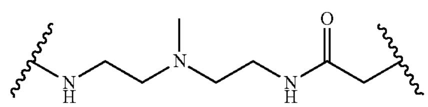


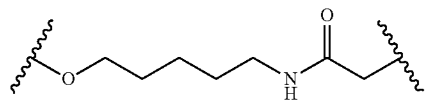


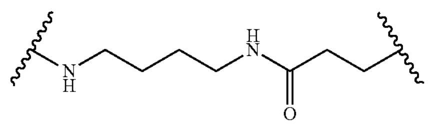


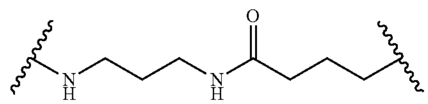


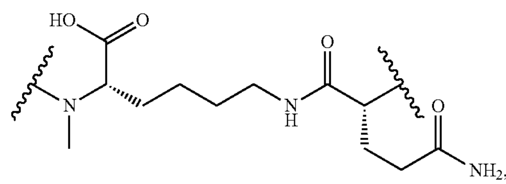
-continued

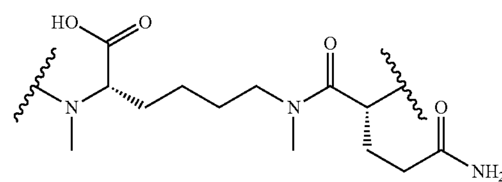


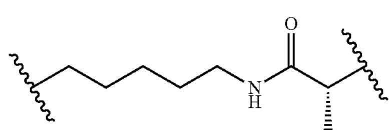


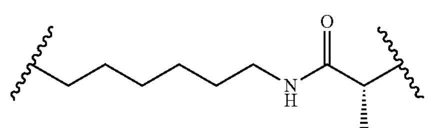


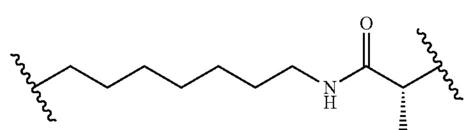


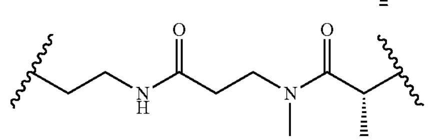


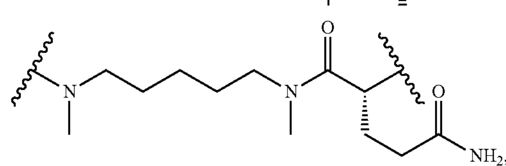


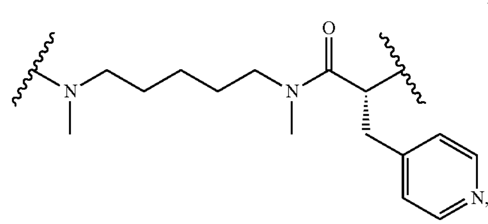




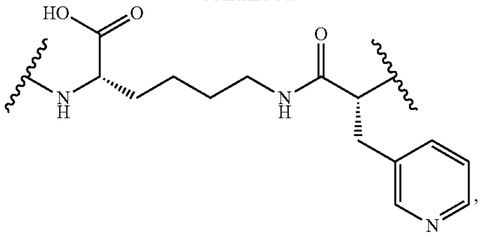


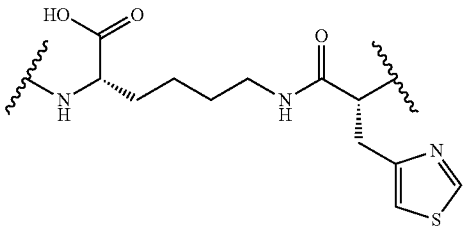


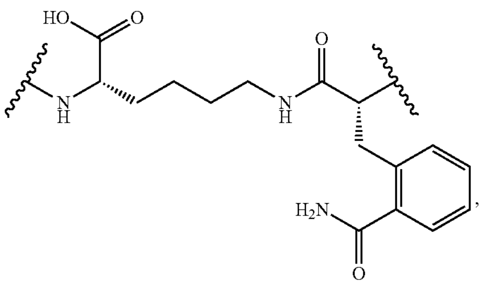


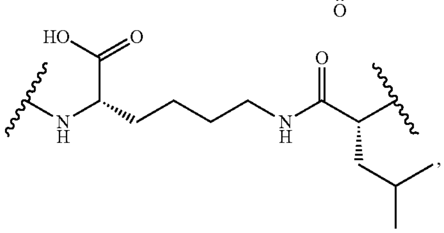


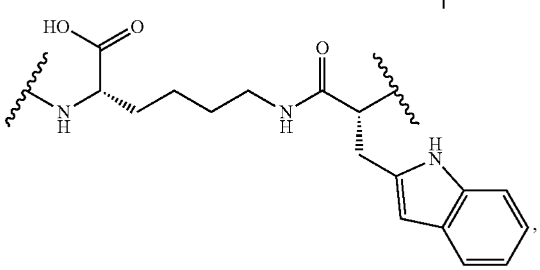
-continued

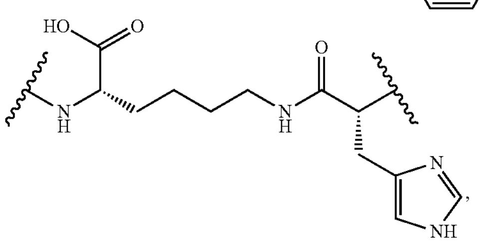


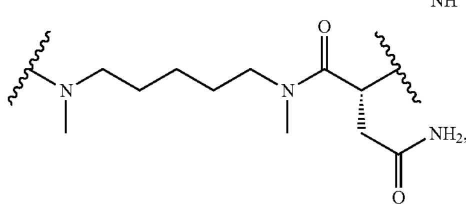


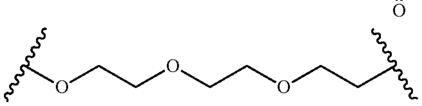






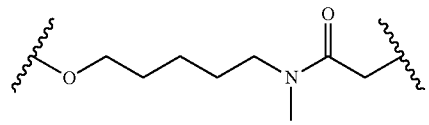




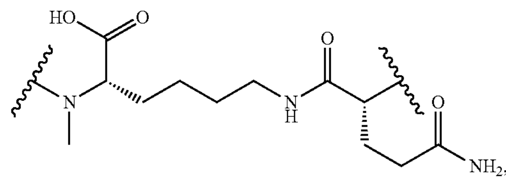


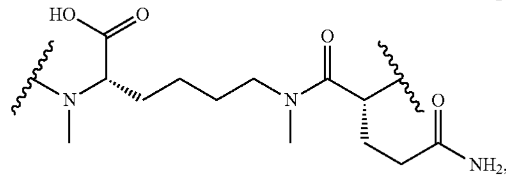
and

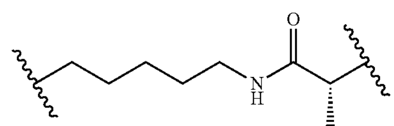
-continued

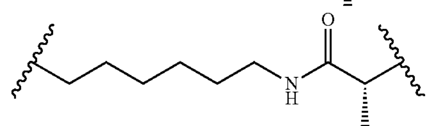


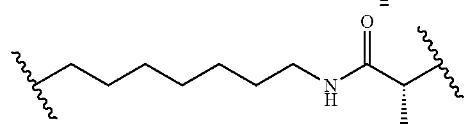
In certain other embodiments, the portion of the compound represented by —R^1-R^2 is selected from

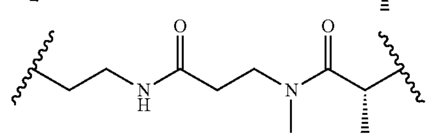


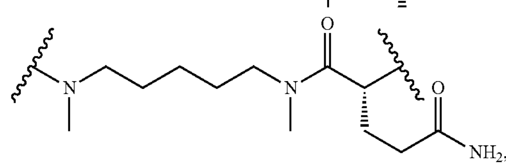


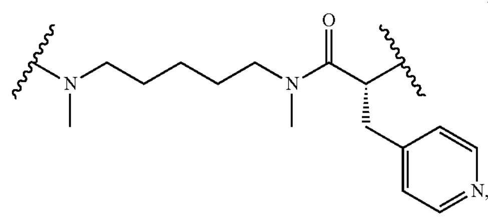


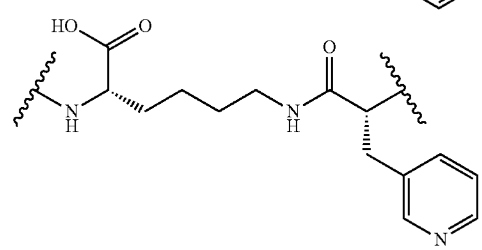




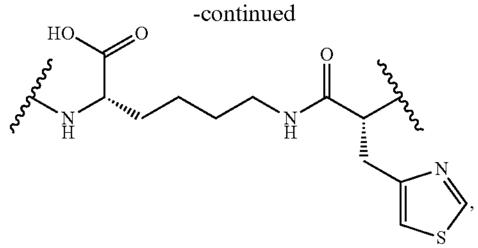


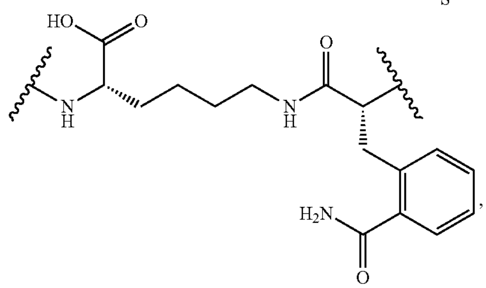


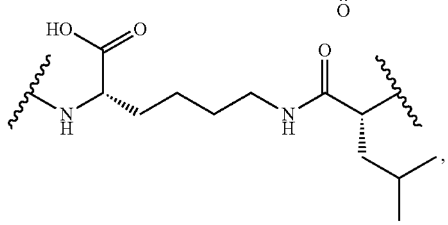


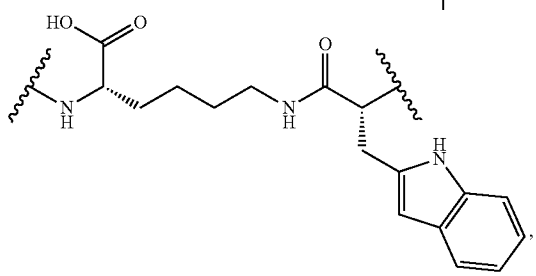


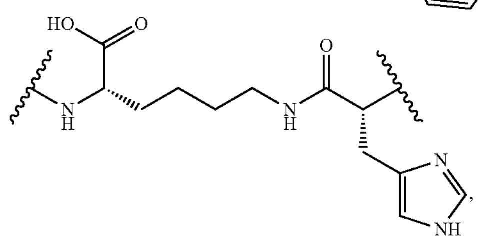
-continued

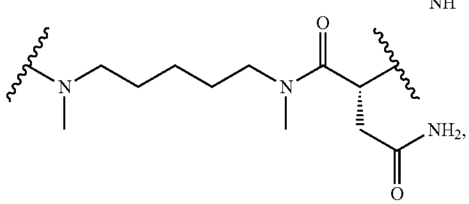


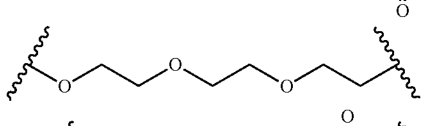




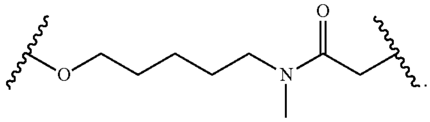








and



In certain embodiments of Formula I, R^3 is —[C(R^d)(R_R^d)]$_{2-4}$—, wherein:

each R^d is independently selected from hydrogen and a suitable alkylene substituent; and any two R^d are optionally

taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl.

In certain embodiments of Formula I, R^3 is †—N(R^{7h})—[C(R^d)(R^d)]$_2$—, wherein:

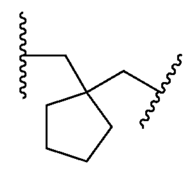
each R^d is independently selected from hydrogen and a suitable alkylene substituent;

any two R^d are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl; and

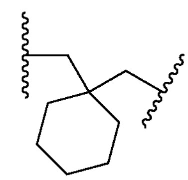
"†" represents a portion of R^3 bound to R^1.

In certain embodiments of Formula I, R^3 is —[C(R^d)(R^d)]—N(R^{7h})—[C(R^d)(R^d)]—, wherein: each R^d is independently selected from hydrogen and a suitable alkylene substituent; and any two R^d are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl.

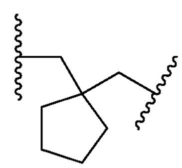
In certain embodiments of Formula I, R^3 is selected from —$(CH_2)_3$—, —CH_2—$C(CH_3)_2$—CH_2—,



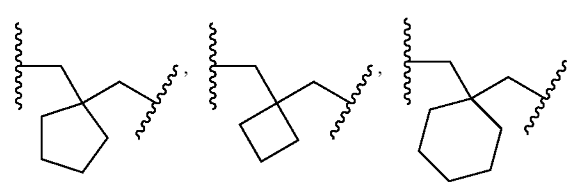
and

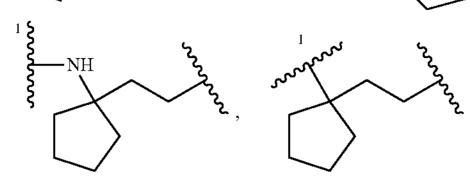


In one aspect of these embodiments, R^3 is

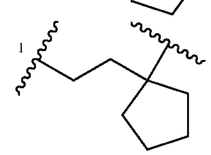


In certain embodiments of Formula I, R^3 is selected from —CH_2—$C(CH_3)_2$—CH_2—, —CH_2—$N(CH_3)$—CH_2—,



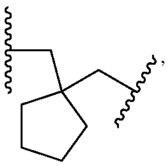
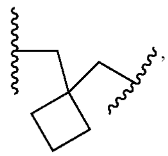
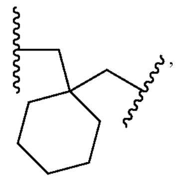
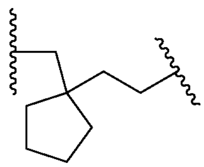
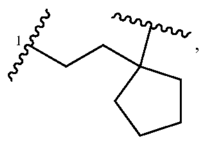
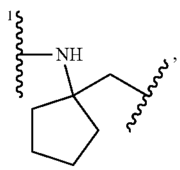
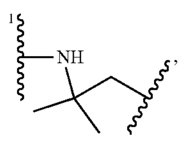
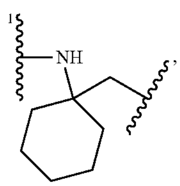
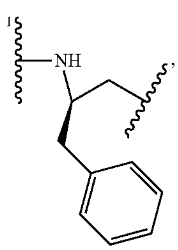


and

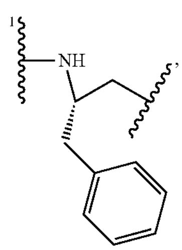


wherein "1" represents a portion of R^3 bound to the carbonyl moiety that is bound to R^1.

In certain embodiments of Formula I, R^3 is selected from —CH_2—$C(CH_3)_2$—CH_2—, —CH_2—$N(CH_3)$—CH_2,

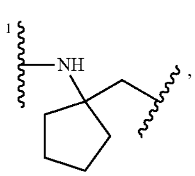
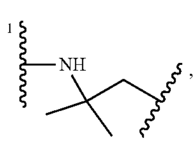
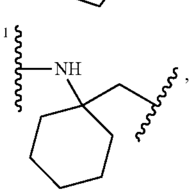
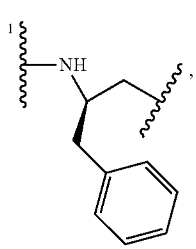










and



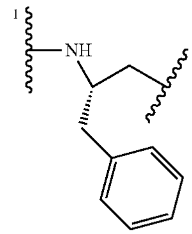
wherein "1" represents a portion of R^3 bound to the carbonyl moiety that is bound to R^1.

In certain other embodiments of Formula I, R^3 is selected from

and

-continued



In certain embodiments of Formula I, each of n and m are independently selected from 0, 1, 2, 3; and n+m is 4 or less.

In certain embodiments of Formula I, R^4 is selected from —$(CH_2)_4$—, and —CH_2-(1,4-phenylene)-†, wherein "†" represents a portion of R^4 bound to $N(R^7)$. In a more specific aspect of these embodiments, R^4 is —CH_2-(1,4-phenylene)-†; and the stereochemistry of the carbon adjacent to R^4 is (S).

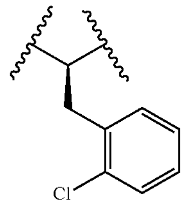
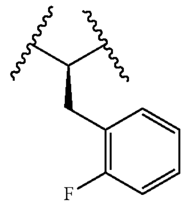
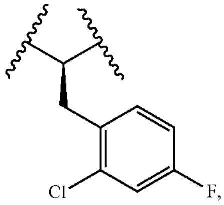
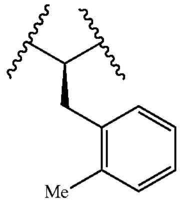
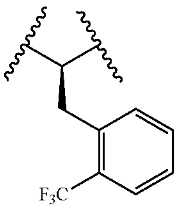
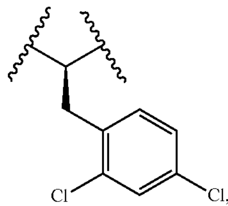
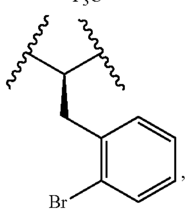
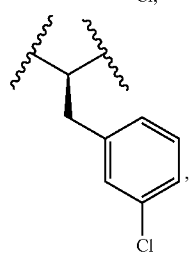
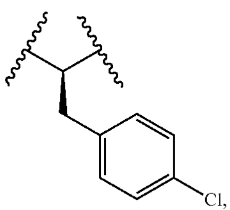
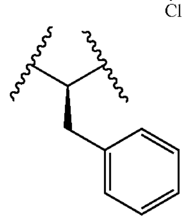
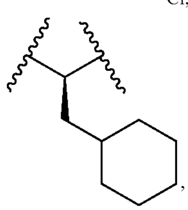
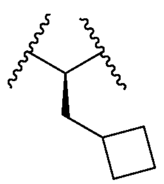
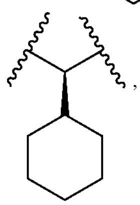
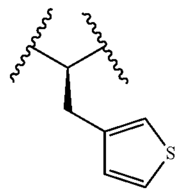
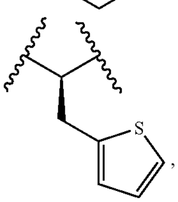
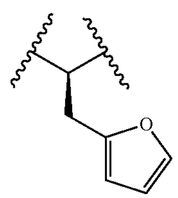
In certain embodiments of Formula I, R^5 is selected from —C(H)(C_1-C_4 alkyl)-, —C(H)(CH_2-aryl)-, —C(H)(CH_2-heteroaryl)-, —C(H)(CH_2-cycloalkyl)-, and —C(H)(cycloalkyl)-, wherein the aryl or heteroaryl is optionally substituted with up to two substituents independently selected from halo, C_1-C_4 alkyl, and phenyl. In one aspect of these embodiments, R^5 is selected from —$C(H)(C(CH_3)_3)$—, —$C(H)(C(H)(CH_2CH_3)CH_3)$—, —$C(H)(C(CH_2CH_3)(CH_3))$—, —C(H)(cyclohexyl)-, —C(H)(CH_2-furanyl)-, —C(H)(CH_2-phenyl)-, —C(H)(CH_2-biphenyl)-, —C(H)(CH_2-thiophenyl)-, —C(H)(CH_2-thiazolyl)-, —C(H)(CH_2-cyclobutyl)-, and —C(H)(CH_2-cyclopropyl)-, wherein any of the furanyl, phenyl, thiophenyl, or thiazolyl are optionally benzofused and optionally substituted with up to two substituents independently selected from fluoro, chloro, bromo, hydroxy and methyl.

In certain embodiments R^5 is —C(H)((R)-benzyl)- wherein a phenyl portion of the benzyl is optionally substituted with up to two substituents independently selected from bromo, chloro, fluoro, methyl, and —CF_3; or R^5 is selected from —C(H)(CH_2—(C_4-C_6 cycloalkyl))-, —C(H)(C_4-C_6 cycloalkyl)-, —C(H)(CH_2-thienyl)-, and —C(H)(CH_2-furanyl)-.

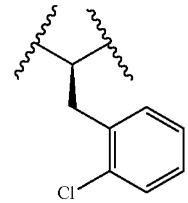
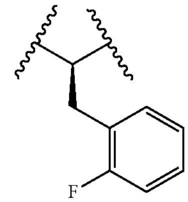
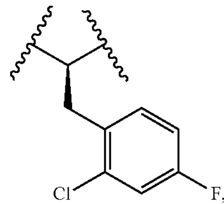
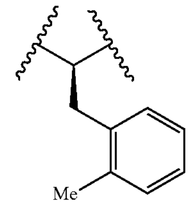
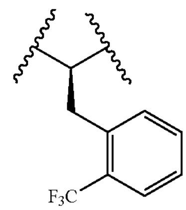
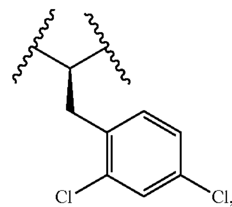
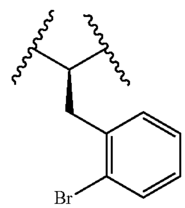
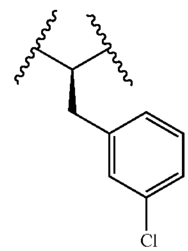
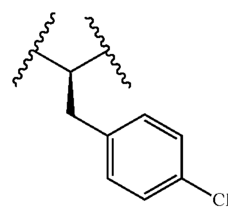
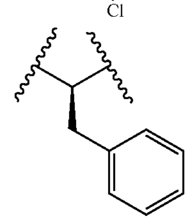
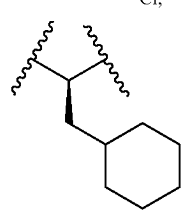
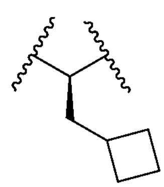
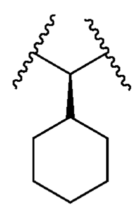
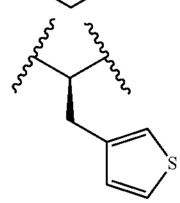
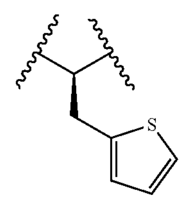
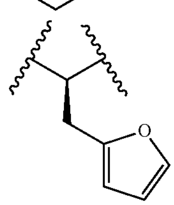
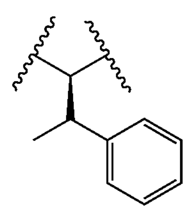
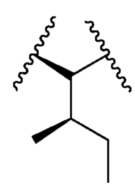
In certain other embodiments, R^5 is selected from —CH((R)-benzyl)-, wherein a phenyl portion of the benzyl is optionally substituted with up to two substituents independently selected from bromo, chloro, fluoro, methyl and —CF_3. In yet other embodiments, R^5 is —C(H)(CH_2—(C_4-C_6 cycloalkyl))-, —C(H)(C_4-C_6 cycloalkyl)-, —C(H)(CH_2-thienyl)-, or —C(H)(CH_2-furanyl)-.

In certain other embodiments, R^5 is —C(H)((R)-benzyl)- wherein a phenyl portion of the benzyl is optionally substituted with up to two substituents independently selected from bromo, chloro, fluoro, methyl, and —CF_3; or R^5 is selected from —C(H)(CH_2—(C_4-C_6 cycloalkyl))-, —C(H)(C_4-C_6 cycloalkyl)-, —C(H)(CH_2-thienyl)-, —C(H)(CH_2-furanyl)-, —C(H)(heterocyclyl)-, —C(H)(CH(CH_3)-(aryl))-, —C(H)(CH(CH_3)-(heteroaryl))-, —C(H)(CH(CH_3)-(heterocyclyl))-, —C(H)(CH(CH_3)-(carbocyclyl))-, and —C(H)(C_3-C_4 alkyl)-.

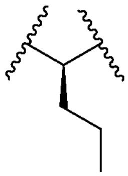
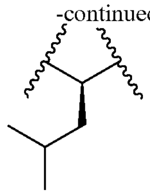
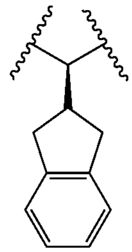
In a more specific embodiment, R^5 is selected from:
















and


In another more specific embodiment, R^5 is selected from:

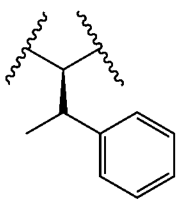
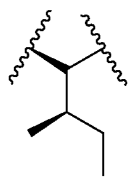
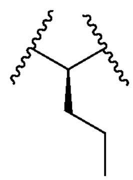
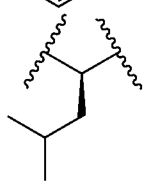
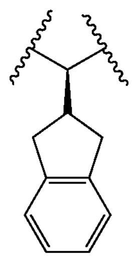



















-continued

,

and
.

In certain other embodiments, R^5 is selected from —C(H)(heterocyclyl)-, —C(H)(CH(CH_3)(aryl))-, —C(H)(CH(CH_3)(heteroaryl))-, —C(H)(CH(CH_3)(heterocyclyl))-, —C(H)(CH(CH_3)(carbocyclyl))-, and —C(H)(C_3-C_4 alkyl)-. In

In certain other embodiments, R^5 is selected from

,
,
,

and
.

In certain embodiments of Formula I, R^6 is selected from heteroaryl, —C(O)—R^8, —C(O)—O—R^8, —C(O)—C(O)—R^8, —S(O)—R^8, —S(O)$_2$—R^8, C(O)—N(R^{7f})—R^8, and —S(O)$_2$—N(R^{7f})—R^8, wherein each R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{7g} is independently selected from hydrogen and C_1-C_4 alkyl; and R^8 is as defined above.

In certain embodiments of Formula I, R^6 is —C(O)—[CH$_2$]$_{0-1}$—R^9; and R^9 is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, and C_1-C_4 alkyl, wherein R^9 is optionally substituted with up to 2 substituents independently selected from halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 hydroxyalkyl. In one aspect of these embodiments, R^9 is selected from phenyl, pyridinyl, oxazolyl, pyrazinyl, pyrimidinyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, —OCH_3, and C_1-C_4 alkyl, wherein any phenyl, pyridinyl, oxazolyl, pyrazinyl, or pyrimidinyl in R^9 is optionally substituted with up to 2 substituents independently selected from fluoro, chloro, CF_3, hydroxy, and —CH_2OH.

In alternate embodiments of Formula I, R^6 is —C(O)—[C(R^{13})$_2$]$_{0-1}$—R^{9a}, wherein R^{9a} is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, C_1-C_4 alkyl, —O—C_1-C_4 alkyl, —NH—CH_3, —N(CH_3)$_2$, and —NH—CH_2-aryl, wherein

any aryl, heteroaryl, cycloalkyl, or saturated heterocyclyl portion of R^{9a} is optionally substituted with up to 2 substituents independently selected from halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, C_1-C_4 alkoxy, —O—(CH$_2$)$_2$-morpholin-4-yl, —N(C_1-C_3 alkyl)$_2$, an N-linked saturated heterocycle, —O—(CH$_2$)$_2$—N(R^{14})—CH$_2$-phenyl, —NH—C(O)—CH$_2$—NH—CH$_2$-phenyl, and —O—(CH$_2$)$_2$—N(R^{14})$_2$;

each R^{13} is independently selected from hydrogen or fluoro, or

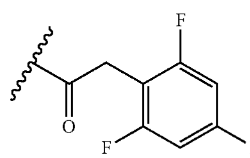
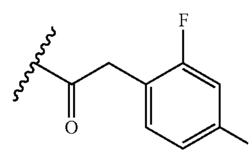
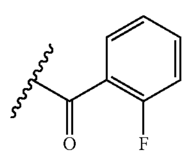
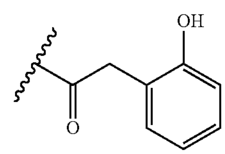
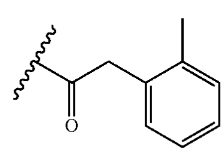
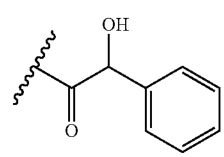
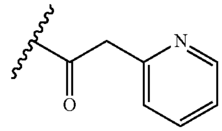
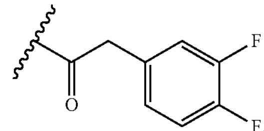
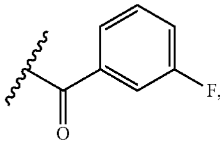
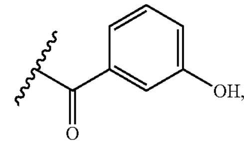
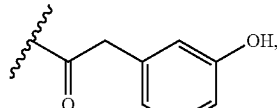
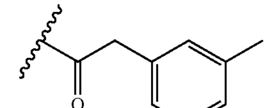
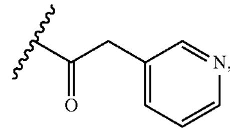
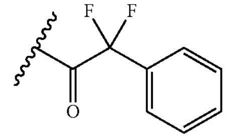
two R^{13} are taken together to form a C_3-C_6 cycloalkyl or =O; and

each R^{14} is independently hydrogen or —CH_3.

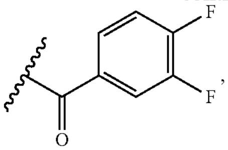
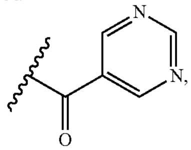
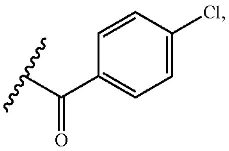
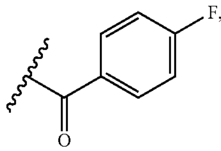
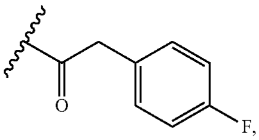
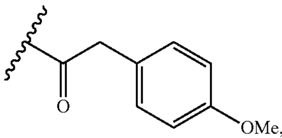
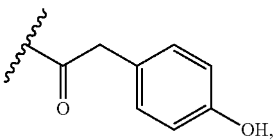
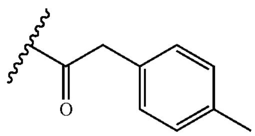
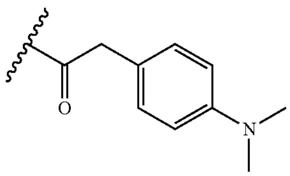
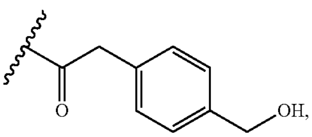
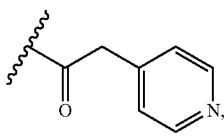
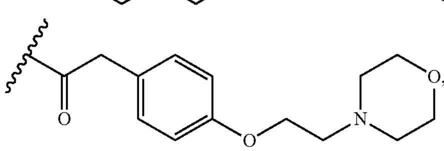
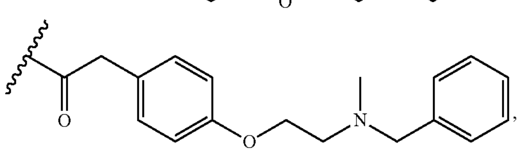
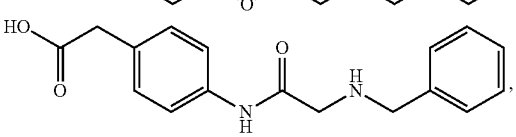
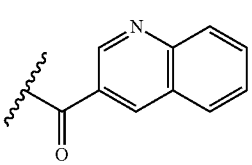
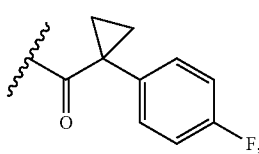
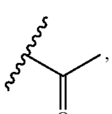
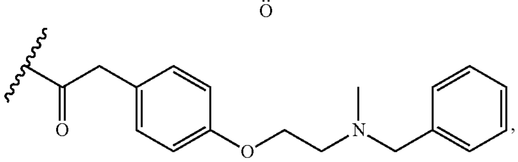
In certain embodiments, R^{9a} is selected from phenyl, pyridyl, quinolinyl, isoquinolinyl, cyclohexyl, 3,3-difluorocyclopropyl, —CH_3, —C(CH_3)$_3$, —OCH_3, —N(CH_3)$_2$, —NH(CH_3), —NH-benzyl, wherein R^{9a} is optionally substituted with up to 2 substituents independently selected from fluoro, chloro, methyl, methoxy, hydroxy, —O—(CH$_2$)$_2$-morpholin-4-yl, —O—(CH$_2$)$_2$—N(CH_3)—CH$_2$-phenyl, and —O—(CH$_2$)$_2$—N(CH_3)$_2$.

In certain embodiments, R^6 is —C(O)-benzyl or —C(O)-phenyl, wherein the benzyl and phenyl in R^6 are each optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, C_1-C_4 alkoxyl, and C_1-C_4 alkyl.

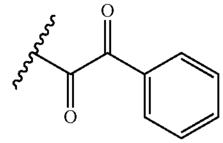
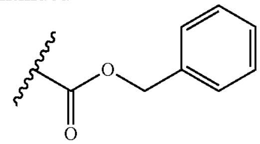
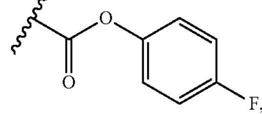
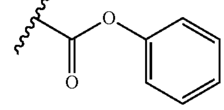
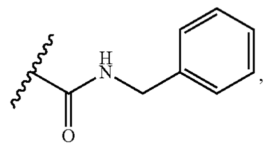
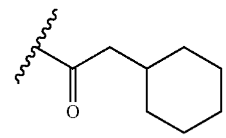
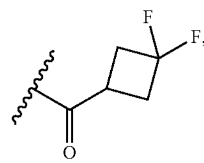
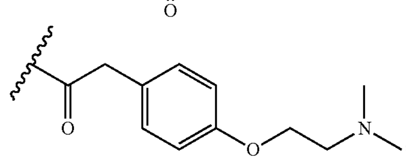
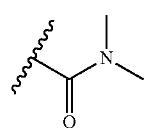
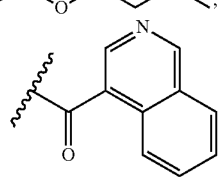
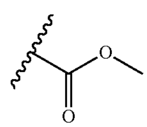
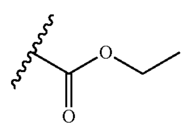
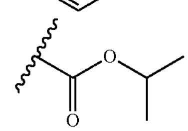
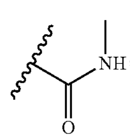
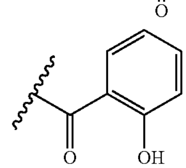
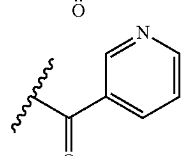
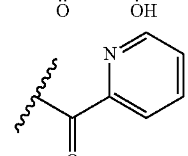
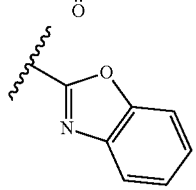
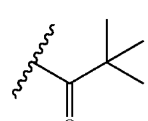
In certain embodiments, R^6 is selected from:

,
,
,
,
,
,
,
,
,
,
,
,
,
,

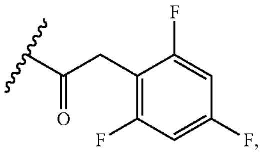
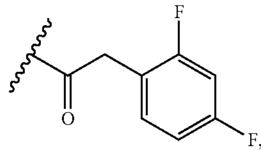
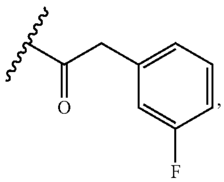
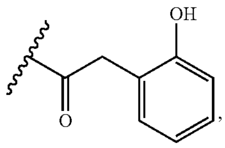
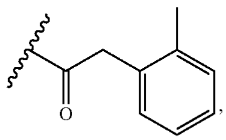
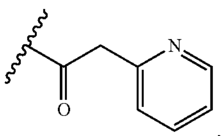
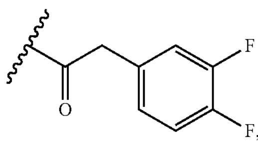
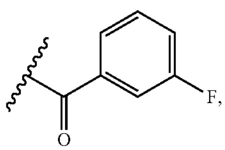
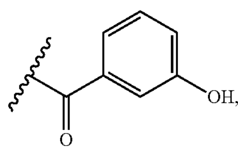
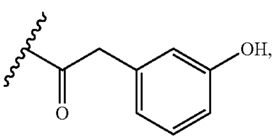
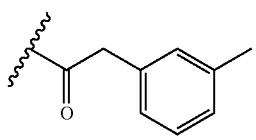
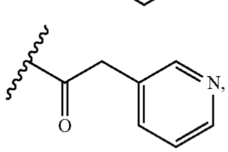
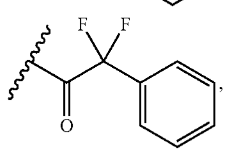
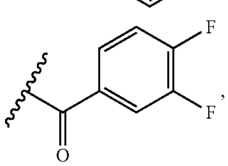
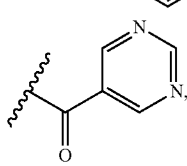
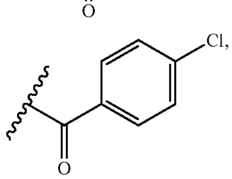
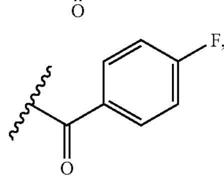
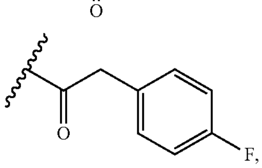
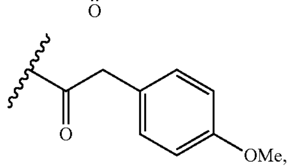
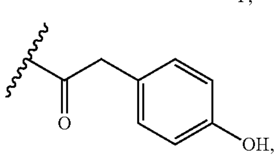
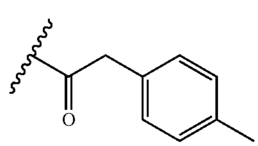
-continued

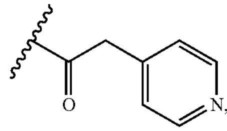
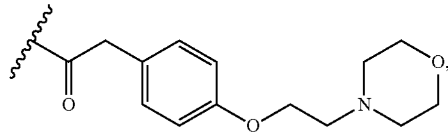
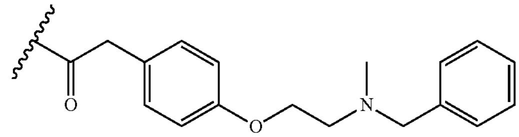
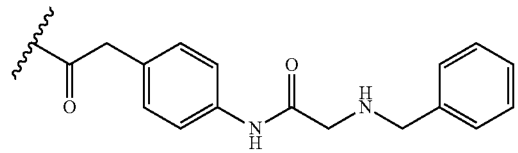
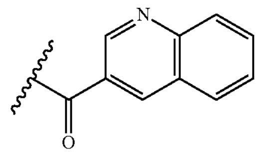
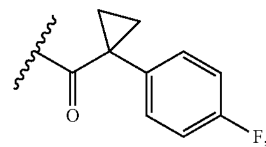
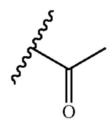
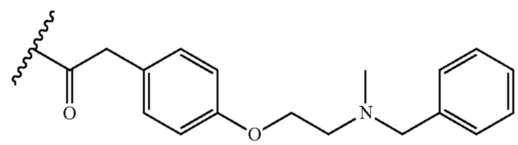
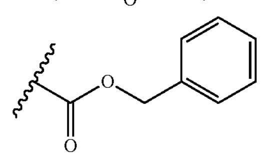
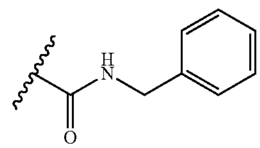
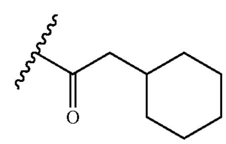
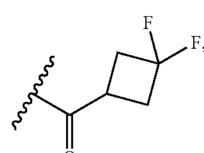
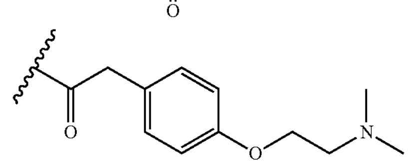
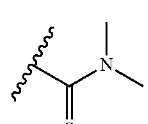
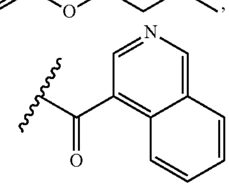
-continued



















and


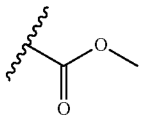
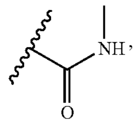
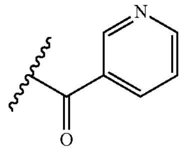
In certain embodiments, R^6 is selected from:

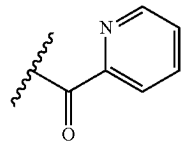






















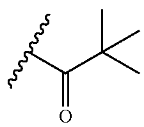
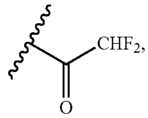
-continued

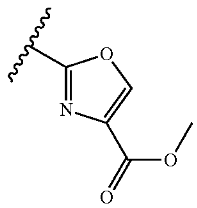
















-continued

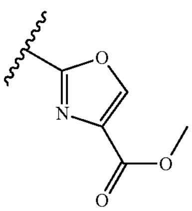
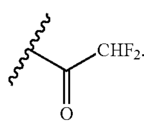
,
,
,

,

,
 and

.

In certain other embodiments, R^6 is selected from

 and .

In certain embodiments of Formula I, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{7g} are independently selected from methyl and hydrogen.

Certain other embodiments relate to a compound of Formula I wherein rather than R^{7d} and R^6 being optionally taken together to form a heterocyclyl, R^{7d} and R^8 are optionally taken together to form a heterocyclyl.

The description above describes multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments.

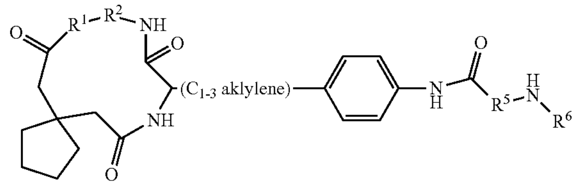
Exemplary specified compounds of Formula I are set forth in FIG. **12**.

In one embodiment, the compound of Formula I is selected from any one of the compounds set forth in FIG. **12**.

Any of the compounds of Formula I, may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H, ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like; N may be in any isotopic form, including ^{14}N and ^{15}N.

In yet other embodiments, the invention provides a compound represented by Formula Ia:

(Ia)



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is —N(H)—;

R^2 is one of the following:

(a) -alkylene-N(H)C(O)-alkylene-ψ,

(b) —C(H)(CO_2H)-alkylene-N(H)C(O)-alkylene-ψ, or

(c) -alkylene-O-alkylene-O-alkylene-ψ; where ψ is a bond to the nitrogen atom in R^1;

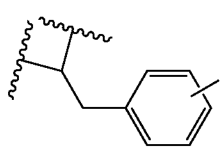
R^5 is C_1-C_2 alkylene substituted with one —(C_1-C_5 alkylene)-aryl that is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl;

R^6 is —C(O)—R^8 or —C(O)—O—R^8;

R^8 is (a) C_1-C_6 alkyl or (b) —(C_1-C_3 alkylene)-aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl.

In certain embodiments, R^2 is -alkylene-N(H)C(O)-alkylene-ψ.

In certain embodiments, R^5 is



In certain embodiments, R^6 is —C(O)—R^8.

In certain embodiments, R^8—(C_1-C_3 alkylene)-aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl. In certain other embodiments, R^8 is benzyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl.

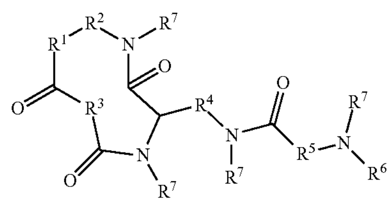
The description above describes multiple embodiments relating to compounds of Formula Ia. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula Ia wherein R^5 is C_1-C_2 alkylene substituted with one —(C_1-C_5 alkylene)-aryl that is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl; and R^6 is —C(O)—O—R^8.

Unless otherwise indicated when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

A. Additional Exemplary Macrocyclic Compounds

An additional family of compounds of the invention is represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from —O— and —N((C_0-C_3 alkylene)-Q)-, wherein Q is selected from hydrogen, —N(R^7), —OH, —O—C_1-C_4 alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R^2 is C_5-C_{12} alkylene, alkenylene or alkynylene, each of which is optionally substituted and wherein:

up to three methylene units of R^2 are optionally and independently replaced with —O—, —N(R^c), —S—, —S(O)—, or —S(O)$_2$—, wherein R^c is selected from hydrogen, C_1-C_4 alkyl, —C(O)—C_1-C_3 alkyl, —C(O)—(C_1-C_3 alkylene)-aryl, —C(O)—(C_1-C_3 alkylene)-heteroaryl, —S(O)$_2$—C_1-C_3 alkyl, —S(O)$_2$—(C_1-C_3 alkylene)-aryl, and —S(O)$_2$—(C_1-C_3 alkylene)-heteroaryl;

any two substituents bound to a common carbon atom in R^2 are optionally taken together to form =O, carbocyclyl or heterocyclyl;

any two substituents bound to different carbon atoms in R^2 are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl; and

any substituent bound to a carbon atom in R^2 and any one R^c are optionally taken together with any intervening atoms to form heteroaryl or heterocyclyl;

R^3 is optionally substituted —(C_2-C_4 alkylene)-, wherein any two substituents on R^3 are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl;

R^4 is —(C_n alkylene)-Y—(C_m alkylene)-, wherein:

each alkylene portion of R^4 is optionally and independently substituted;

Y is selected from aryl, heteroaryl, carbocyclyl, heterocyclyl and optionally substituted C_1-C_3 alkylene;

each of n and m are independently selected from 0, 1, 2, 3, 4, 5 and 6; and

n+m is 6 or less;

R^5 is C_1-C_2 alkylene substituted with one or more —(C_0-C_5 alkylene)-R^f, wherein each R^f is independently selected from —CH_3, —O—C_1-C_3 alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R^6 is selected from heteroaryl, —C(O)—R^8, —S(O)—R^8, —S(O)$_2$—R^8, —C(O)—N(R^7)—R^8, and —S(O)$_2$—N(R^7)—R^8;

each R^7 is independently selected from hydrogen and C_1-C_4 alkyl;

R^8 is selected from —(C_0-C_6 alkylene)-aryl, —(C_0-C_6 alkylene)-heteroaryl, —(C_0-C_6 alkylene)-carbocyclyl, —(C_0-C_6 alkylene)-heterocyclyl, and C_1-C_6 alkyl, wherein when R^8 is C_1-C_6 alkyl, up to two methylene units in the alkyl are optionally and independently replaced with —O—, —N(R^7), —S—, —S(O)—, or —S(O)$_2$—; and

any alkyl or alkylene portion of R^8 is optionally substituted with an appropriate alkyl or alkylene substituent other than =O; or

R^7 and R^8 are optionally taken together to form a heterocyclyl; and

any aryl, heteroaryl, carbocyclyl or heterocyclyl portion of the compound is optionally substituted.

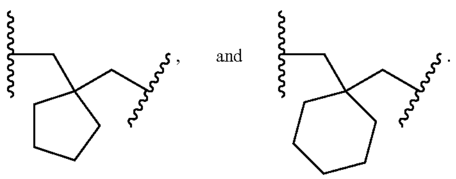
It will be understood by those of skill in the art that because the compounds of the invention are limited to compounds that are stable, compounds formed by the optional and independent replacement of up to three methylene units in R^2 with certain combinations of —O—, —S—, —S(O)—, —S(O)$_2$—, or —NR^c— are not within the scope of the present invention. For example, compounds wherein the R^2 moiety comprises an —O—, —S—, —S(O)—, —S(O)$_2$, or —N(R^c)—, adjacent to an —O—, —S—, —S(O)—, —S(O)$_2$, or —N(R^c)— are not within the scope of the present invention, except for an —S(O)$_2$— adjacent a —N(R^c)—. In addition, R^2 should not comprise —O—CH_2—O—, —N—CH_2—O—, or —O—CH_2—N—, wherein the —CH_2— portion thereof is optionally substituted, except when the —CH_2— portion is substituted to become —C(O)—.

In certain embodiments of Formula II, R^1 is selected from —O—, —NH— and —N(C_1-C_4 alkyl-OH)—. In one aspect of these embodiments, R^1 is selected from —O—, —NH— and —N(CH_2CH_2OH)—.

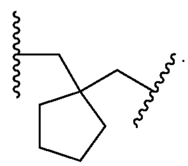
In certain embodiments of Formula II, R^2 is selected from *—C(H)(R^{10}—(CH_2)$_{2-4}$—N(H)—C(O)—(C(R^{11})$_2$)$_{1-5}$—, *—C(H)(R^{10})—(CH_2)$_{4-8}$—, *—C(H)(R^{10})—(CH_2)$_{2-4}$-(1,4-phenylene)-N(H)—C(O)—(C(R^{11})$_2$)$_{1-3}$—, and *—C(H)(R^{10})—(CH_2)$_{2-4}$-(1,4-phenylene)-; R^{10} is selected from hydrogen, —C(O)—O—C_1-C_4 alkyl, and —C(O)—OH; and each R^{11} is independently selected from hydrogen, benzyl, C_1-C_4 alkyl and C_1-C_4 hydroxyalkyl, wherein no more than two R^{11} are other than hydrogen; one methylene unit in a specified —(CH_2)$_{2-4}$ or —(CH_2)$_{4-8}$ portion of R^2 is optionally replaced with —N(R^7); and "*" represents a terminus of R^2 bound to R^1. In one aspect of these embodiments, R^2 is selected from *—C(H)(R^{10})—(CH_2)$_{2-4}$—N(H)—C(O)—(CH_2)$_{1-5}$—, *—C(H)(R^{10})—(CH_2)$_4$—, *—C(H)(R^{10})—(CH_2)$_{2-4}$—N(H)—C(O)—C((CH_3)$_2$)—, *—C(H)(R^{10})—(CH_2)$_{2-4}$—N(H)—C(O)—C(H)(CH_2OH)—, *—C(H)(R^{10})—CH_2-(1,4-phenylene)-N(H)—C(O)—(CH_2)$_{1-3}$—, *—C(H)(R^{10})—CH_2-(1,4-phenylene)-, —(CH_2)$_8$—, *—(CH_2)$_2$—N(CH_3)—(CH_2)$_2$—N(H)—C(O)—CH_2—, and *—(CH_2)$_5$—N(H)—C(O)—C(H)(benzyl)-; and R^{10} is selected from hydrogen, —C(O)—O—CH_3, and C(O)—OH.

The term "specified —(CH_2)$_{2-4}$— or —(CH_2)$_{4-8}$— portion of R^2" as used in the preceding paragraph refers to the portion of those choices for R^2 that are indicated as —(CH_2)$_{2-4}$— or —(CH_2)$_{4-8}$—. For example, when R^2 is —C(H)(R^{10})—(CH_2)$_{2-4}$—N(H)—C(O)—(CH_2)$_{1-5}$—, only the bolded portion is a "specified —(CH_2)$_{2-4}$— portion of R^2."

In certain embodiments of Formula II, R^3 is selected from —$(CH_2)_3$—. —CH_2—$C(CH_3)_2$—CH_2—,



In one aspect of these embodiments, R^3 is



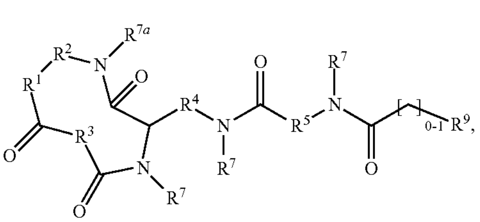
In certain embodiments of Formula II, R^4 is selected from —$(CH_2)_4$—*, and —CH_2-(1,4-phenylene)-*, wherein "*" represents a portion of R^4 bound to $N(R^7)$.

In certain embodiments of Formula II, R^5 is selected from —CH—(C_1-C_4 alkyl), —CH—CH_2-aryl, —CH—CH_2-heteroaryl, —CH—CH_2-cycloalkyl, and —CH-cycloalkyl, wherein the aryl or heteroaryl is optionally substituted with up to two substituents independently selected from halo, C_1-C_4 alkyl, and phenyl. In one aspect of these embodiments, R^5 is selected from —CH—$C(CH_3)_3$, —CH—CH(CH_2CH_3)—CH_3, —CH-cyclohexyl, —CH—CH_2-furanyl, —CH—CH_2-phenyl, —CH—CH_2-biphenyl, —CH—CH_2-thiophenyl, —CH—CH_2-thiazolyl, —CH—CH_2-cyclobutyl, and —CH—CH_2-cyclopropyl, wherein any of the furanyl, phenyl, thiophenyl or thiazolyl is optionally benzofused and optionally substituted with up to two substituents independently selected from fluoro, chloro, bromo, hydroxy and methyl.

In certain embodiments of Formula II, R^6 is —C(O)—$[CH_2]_{0\text{-}1}$—R^9; and R^9 is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, and C_1-C_4 alkyl, wherein R^9 is optionally substituted with up to 2 substituents independently selected from halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 hydroxyalkyl. In one aspect of these embodiments, R^9 is selected from phenyl, pyridinyl, oxazolyl, pyrazinyl, pyrimidinyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, —OCH_3, and C_1-C_4 alkyl, wherein any phenyl, pyridinyl, oxazolyl, pyrazinyl, or pyrimidinyl in R^9 is optionally substituted with up to 2 substituents independently selected from fluoro, chloro, CF_3, hydroxy, and —CH_2OH.

In certain embodiments of Formula II, each R^7 is independently selected from methyl and hydrogen.

In certain embodiments, the invention provides a compound of Formula IIa:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from —O—, —NH— and —N(C_1-C_4 alkyl-OH)—;

R^2 is selected from *—C(H)(R^{10})—$(CH_2)_{2\text{-}4}$—N(H)—C(O)—$(C(R^{11})_2)_{1\text{-}5}$—, *—C(H)($R^{10}$)—$(CH_2)_{4\text{-}8}$—, *—C(H)($R^{10}$)—$(CH_2)_{2\text{-}4}$-(1,4-phenylene)-N(H)—C(O)—$(C(R^{11})_2)_{1\text{-}3}$—, and *—C(H)($R^{10}$)—$(CH_2)_{2\text{-}4}$-(1,4-phenylene)-; wherein:

R^{10} is selected from hydrogen, —C(O)—O—C_1-C_4 alkyl, and —C(O)—OH;

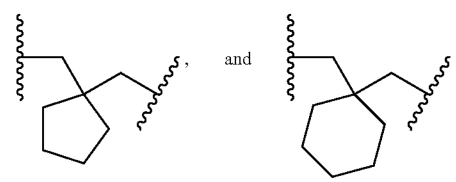
each R^{11} is independently selected from hydrogen, benzyl, C_1-C_4 alkyl and C_1-C_4 hydroxyalkyl;

no more than two R^{11} are other than hydrogen;

one methylene unit in a specified —$(CH_2)_{2\text{-}4}$ or —$(CH_2)_{4\text{-}8}$ portion of R^2 is optionally replaced with —N(R^7); and

"*" represents a terminus of R^2 bound to R^1;

R^3 is selected from —$(CH_2)_3$—, —CH_2—$C(CH_3)_2$—CH_2—,



R^4 is selected from —$(CH_2)_4$—*, and —CH_2-(1,4-phenylene)-*

R^5 is selected from —CH—(C_1-C_4 alkyl), —CH—CH_2-aryl, —CH—CH_2-heteroaryl, —CH—CH_2-cycloalkyl, and —CH-cycloalkyl, wherein the aryl or heteroaryl is optionally substituted with up to two substituents independently selected from halo, C_1-C_4 alkyl, and phenyl; and

each R^7 is independently selected from hydrogen and C_1-C_4 alkyl;

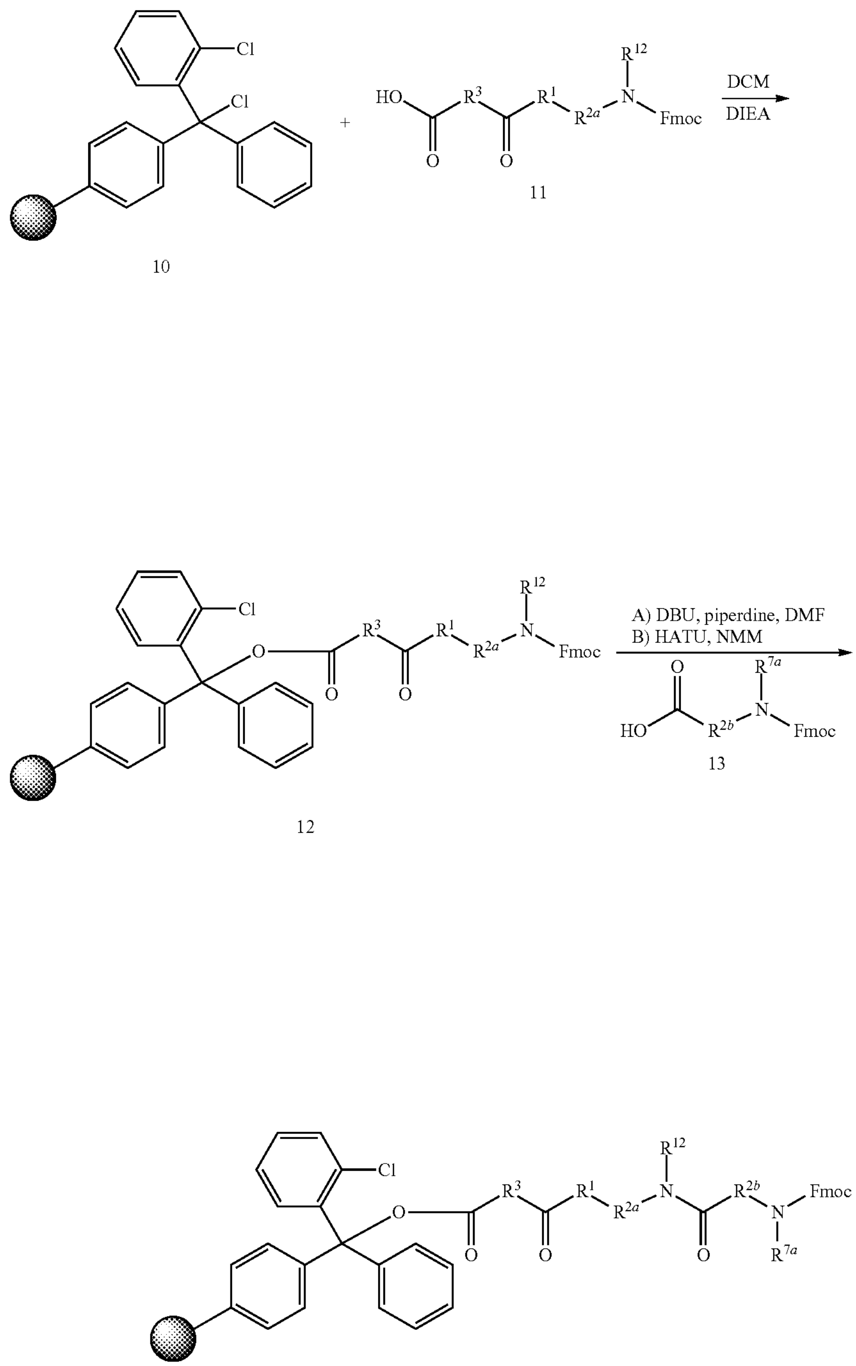
R^9 is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, and C_1-C_4 alkyl, wherein R^9 is optionally substituted with up to 2 substituents independently selected from halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, C_1-C_4 alkoxy, and C_1-C_4 hydroxyalkyl.

II. METHODS OF SYNTHESIZING COMPOUNDS OF THE INVENTION

The compounds of the present invention can be prepared using an iterative peptide coupling procedure as illustrated in following synthetic schemes. Exemplary general synthetic protocols are presented in Schemes 1 through 4. The schemes and accompanying description of synthetic procedures are given for the purpose of illustrating the invention, and should not be construed as limiting the scope or spirit of the invention.

Abbreviations as used herein include O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); diisopropylethylamine (DIPEA); dimethylformamide (DMF); 9-fluorenylmethoxycarbonyl (Fmoc); methanol (MeOH); methylene chloride (DCM); tert-butoxycarbonyl (Boc); tert-butyl (tBu); tetrahydrofuran (THF); trifluoroacetic acid (TFA); 1,8-diazobicyclo[5.4.0]-undec-7-ene (DBU); N-methylmorpholine (NMM); 1-hydroxy-7-azabenzotriazole (HOAt); phenyl (Ph); trifluoroacetic acid (TFA); triethylamine (Et_3N); petroleum ether (PE); ethyl acetate (EA); acetic acid (AcOH); diethyl ether (Et_2O); Boc anhydride ($(Boc)_2O$); dimethylsulfoxide (DMSO); diisopropylethylamine (DIEA); N-bromosuccinimide (NBS); trityl chloride (TrtCl); triphenyl phosphate (PPh_3); (9H-fluoren-9-yl)methyl (2,5-dioxopyrrolidin-1-yl) carbonate (Fmoc-Osu); room temperature (r.t. or RT); and thin-layer chromatography (TLC).

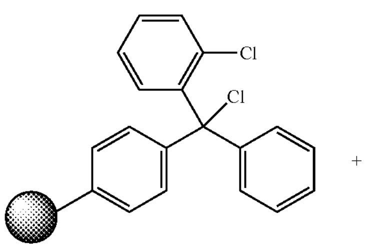
SCHEME 1.



14

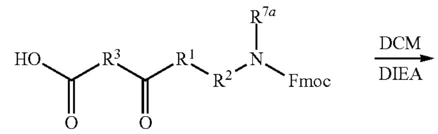
Scheme 1 depicts a general synthesis method for an intermediate to compounds of Formula I, wherein R^2 is *—CH(R^{10})—X—CH(R^{10})—N(R^{12})—C(O)—CH(R^{11})—$(CH_2)_{0-2}$—, as defined for Formula I. In Scheme 1, R^{2a} represents the *—CH(R^{10})—X—CH(R^{10})— terminal portion of R^2, and R^{2b} represents the —CH(R^{11})—$(CH_2)_{0-2}$- terminal portion of R^2. A 2-chloro-trityl chloride resin 10 is combined with an appropriate protected alkylamino acetic acid 11 in DCM to form resin 12. Resin 12 is then deprotected with DBU and piperidine in DMF and then coupled to a protected amino acid 13 using HATU and NMM to produce resin 14, which is further coupled according to Scheme 3, below.

SCHEME 2.

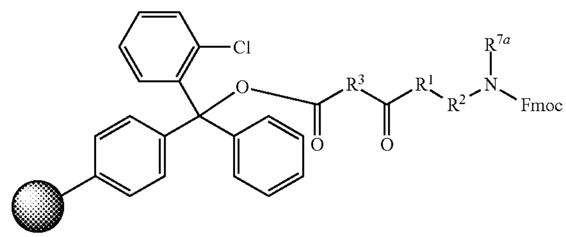


10

-continued



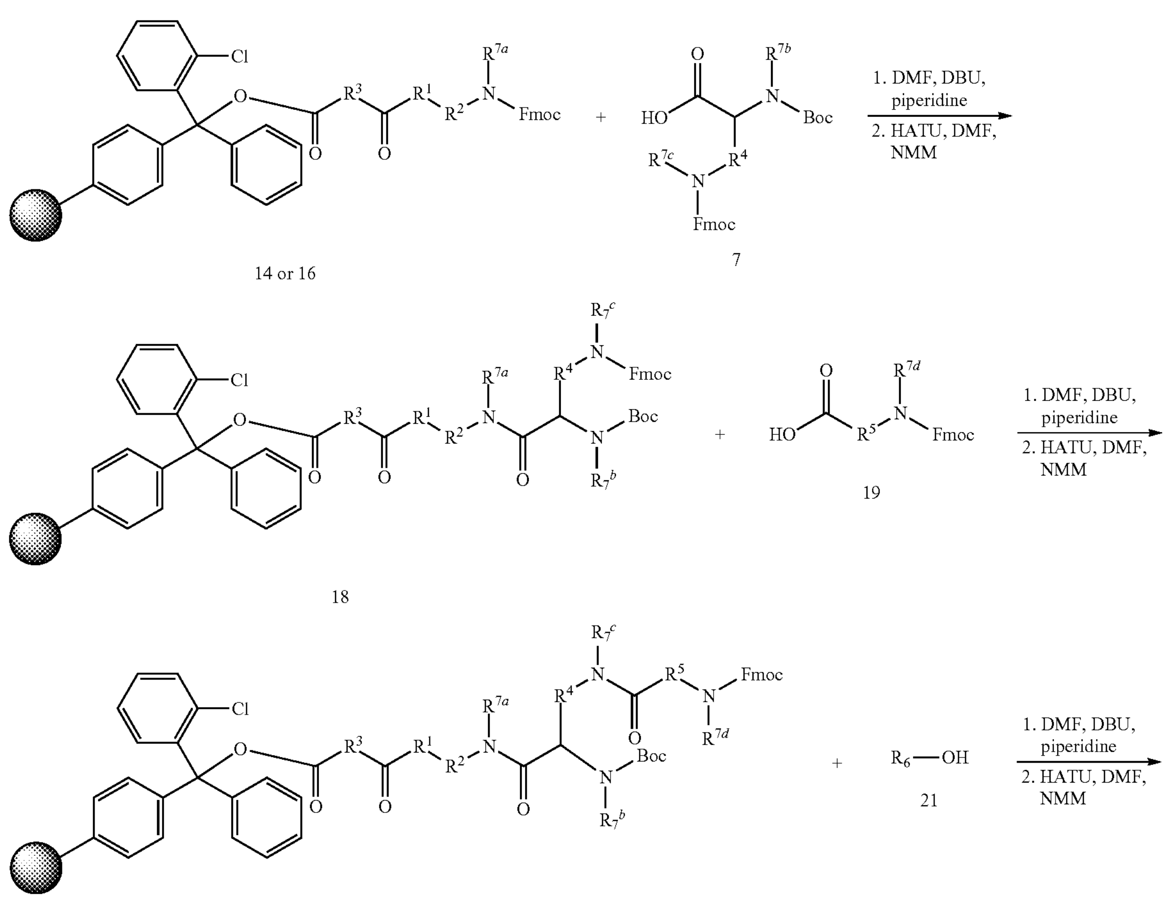
15



16

Scheme 2 depicts a general synthesis method for an intermediate to compounds of Formula I, wherein R^2 is *—CH(R^{10})—Z—. A 2-chloro-trityl chloride resin 10 is combined with an appropriate protected alkylamino acetic acid 15 in DCM to form resin 16, which is further coupled according to Scheme 3, below.

SCHEME 3.



14 or 16

7

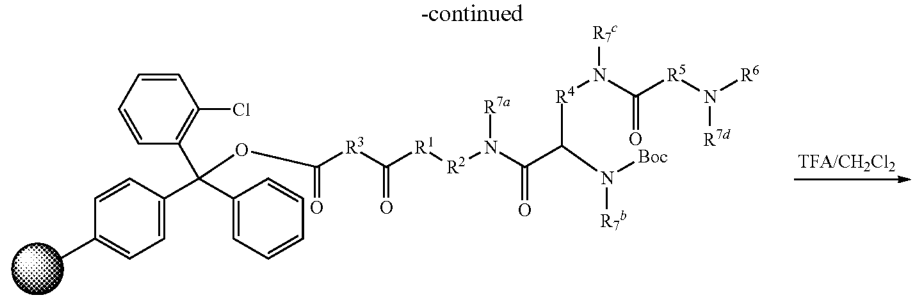
18

19

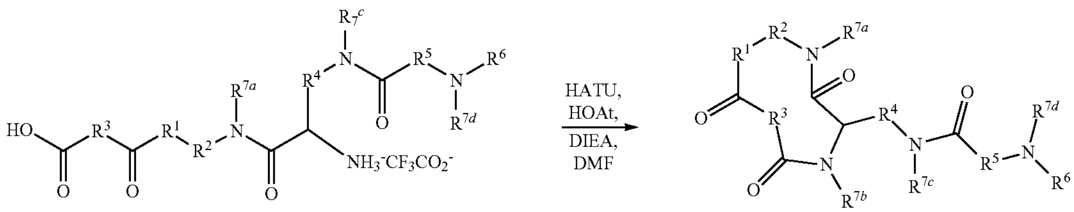
20

21

-continued



22

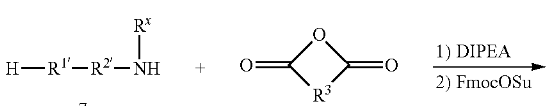


23

Formula I

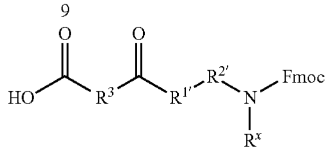
Scheme 3 depicts a general synthesis for compounds of Formula I, starting with intermediate 14 from Scheme 1 or intermediate 16 from Scheme 2. The structures of intermediates 14 and 16 are shown in the scheme for convenience. Each R^7 depicted in Scheme 3 is independently selected from hydrogen and C_1-C_4 alkyl. Intermediate 14 or intermediate 16 is deprotected with DBU and piperidine in DMF and then coupled to the appropriate N,N'-orthogonally-protected diamino acid 17. The Fmoc group of 17 is removed again with DBU and piperidine in DMF and the resulting deprotected resin is coupled to amino acid 19. The deprotection/coupling process is repeated to add acid 21. Reaction of compound 22 with TFA/CH_2Cl_2 removes the Boc protecting group and hydrolyzes the ester bond to the resin to form intermediate 23, which is cyclized using HATU, HOAt, DIEA and DMF to form a compound of Formula I.

SCHEME 4A



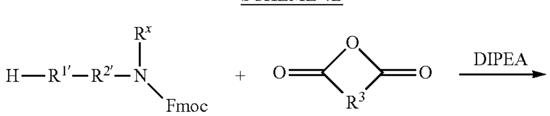
7

9



11 or 15

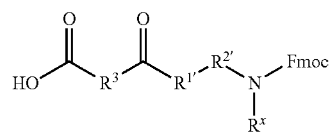
SCHEME 4B



8

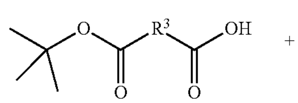
9

-continued

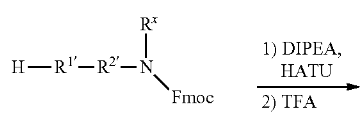


11 or 15

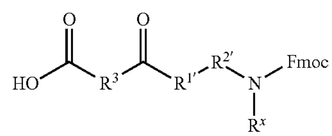
SCHEME 4C



40

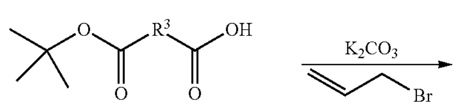


8



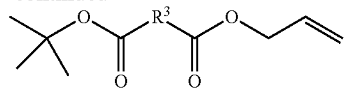
11 or 15

SCHEME 4D

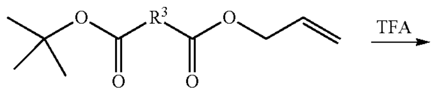


40

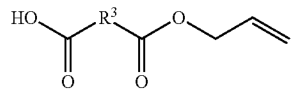
-continued



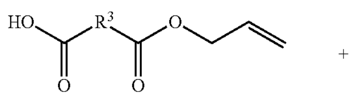
41



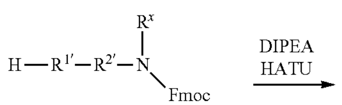
41



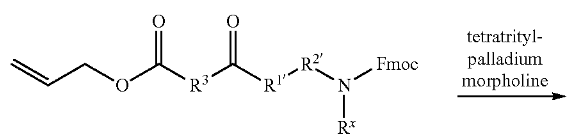
42



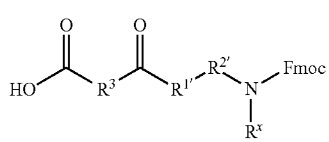
42



8



43

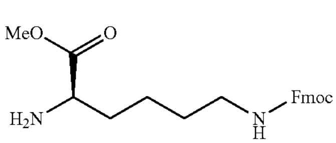


11 or 15

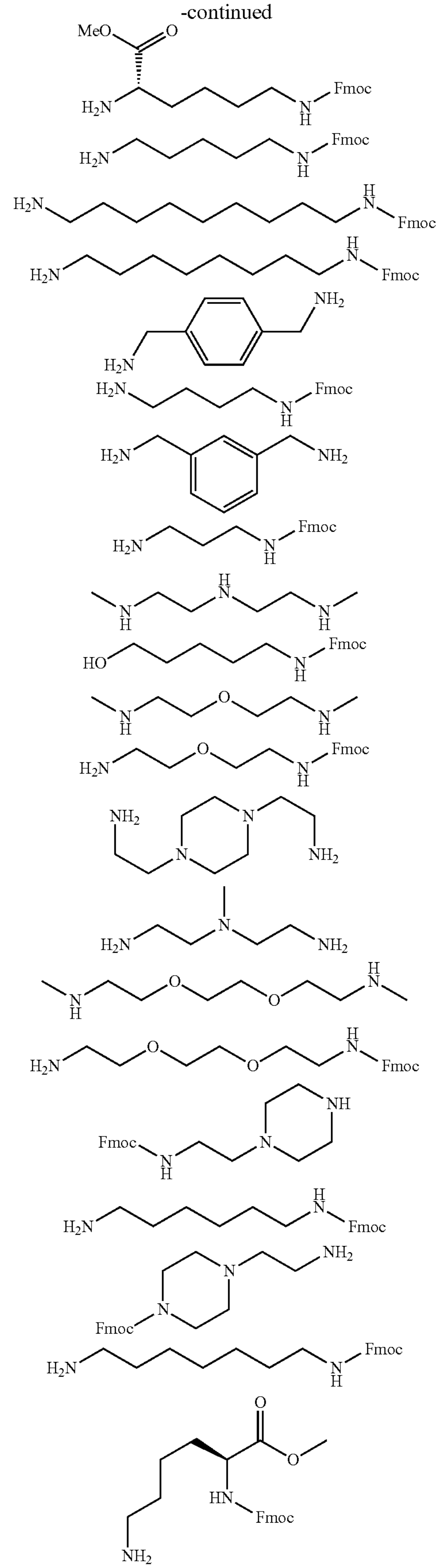
Schemes 4A and 4B depict the synthesis of intermediate 11 or 15 when R^3 is symmetrical. In these schemes, $R^{1'}$ is —N(C_0-C_3 alkylene-Q)-. When R^2 in a compound of Formula I is *—CH(R^{10})—Z—, $R^{2'}$ is *—CH(R^{10})—Z— and R^x is R^{7a}. When R^2 is *—CH(R^{10})—X—CH(R^{10})—N(R^{12})—C(O)—CH(R^{11})—$(CH_2)_{0-2}$—, R^{2a} represents the *—CH(R^{10})—X—CH(R^{10})— portion of R^2 and R^x is R^{12}. Scheme 4A was utilized when H—$R^{1'}$—$R^{2'}$—NH(R^x)— was a symmetrical moiety. Otherwise, Scheme 4B was utilized.

In Scheme 4A, amine reagent 7 is combined with the dioxo cyclic reagent 9 in the presence of DIPEA. The resulting amine is then protected by reaction with FmocOSu to produce intermediate 11 or 15. In Scheme 4B, protected amine 8 is reacted with the dioxo cyclic reagent 9 in the presence of DIPEA to produce intermediate 11 or 15.

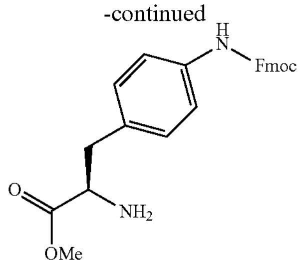
A wide variety of reagents 7 and 8 are commercially available, including the following:

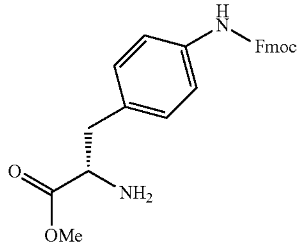


-continued



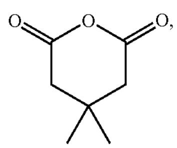
-continued

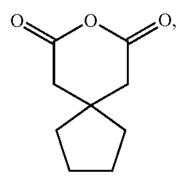


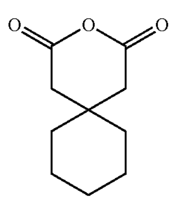


If additional or alternate protection of reactive groups in such commercially available reagents is required (Fmoc and/or Boc protection; Boc deprotection, methyl esterification), it may be achieved by standard protection protocols well known in the art.

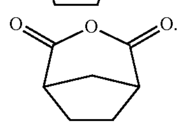
Similarly, a variety of reagents 9 are commercially available including,







and



Schemes 4C and 4D depict the synthesis of intermediate 11 or 15 when R^3 is asymmetrical. In these schemes, $R^{1'}$ is —N(C_0-C_3 alkylene-Q)-. When R^2 in a compound of Formula I is *—CH(R^{10})—Z—, $R^{2'}$ is *—CH(R^{10})—Z— and R^x is R^{7a}. When R^2 is *—CH(R^{10})—X—CH(R^{10})—N(R^{12})—C(O)—CH(R^{11})—(CH_2)$_{0\text{-}2}$—, R^{2a} represents the *—CH(R^{10})—X—CH(R^{10})— portion of R^2 and R^x is R^{12}.

In Scheme 4C, protected amine 8 is reacted with carboxylic acid 40 in the presence of DIPEA and HATU, followed by treatment with TFA to produce intermediate 11 or 15.

In Scheme 4D, carboxylic acid 40 is converted to allyloxycarbonyl carboxylic acid 41 by reaction with 3-bromopropene and K_2CO_3. The allyloxycarbonyl carboxylic acid 41 is then reacted with TFA to produce 42, which is then reacted with amine 8 in the presence of DIPEA and HATU to produce allyl intermediate 43. Intermediate 43 is then converted to intermediate 11 or 15 by treatment with tetratritylpalladium and morpholine.

Different t-butyl protected carboxylic acids 40 can be synthesized by reacting an appropriate alkyl carboxylic acid or cycloalkyl carboxylic acid with tert-butyl acrylate. This is shown in more detail in the Examples.

Combinations of substituents and variables contemplated by the present invention are only those that result in the formation of compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

III. THERAPEUTIC APPLICATIONS

The compounds and pharmaceutical compositions of the present invention are useful in treating or preventing any disease or condition that is mediated directly or indirectly by IL-17. Such diseases include inflammatory diseases and conditions, proliferative diseases (e.g., cancer), autoimmune diseases and other disease described herein.

Increased levels of IL-17 (i.e., IL-17A) have been associated with several conditions including airway inflammation, rheumatoid arthritis (RA), osteoarthritis, bone erosion, intraperitoneal abscesses and adhesions, inflammatory bowel disorder (IBD), allograft rejection, psoriasis, psoriatic arthritis, ankylosing spondylitis, certain types of cancer, angiogenesis, atherosclerosis and multiple sclerosis (MS). Both IL-17 and IL-17R are upregulated in the synovial tissue of RA patients. IL-17 exerts its role in pathogenesis of RA through IL-1-β and TNF-α dependent and independent pathways. IL-17 stimulates secretion of other cytokines and chemokines, e.g., TNF-α, IL-1β, IL-6, IL-8 and Gro-α. IL-17 directly contributes to disease progression in RA. Injection of IL-17 into the mouse knee promotes joint destruction independently of IL-I β activity (Ann Rheum Dis 2000, 59:529-32). Anti-IL-1β antibody has no effect on IL-17 induced inflammation and joint damage (J Immunol 2001, 167:1004-1013). In an SCW-induced murine arthritis model, IL-17 induced inflammatory cell infiltration and proteoglycan depletion in wild-type and IL-1β knockout and TNF-α knockout mice. IL-17 knockout mice are phenotypically normal in the absence of antigenic challenge, but have markedly reduced arthritis following type II collagen immunization (J Immunol 2003, 171:6173-6177).

Increased levels of IL-17-secreting cells have also been observed in the facet joints of patients suffering from ankylosing spondylitis (H Appel et al., Arthritis Res Therap 2011, 13:R95).

Multiple sclerosis is an autoimmune disease characterized by central nervous system (CNS) inflammation with damage to the myelin sheath surrounding axons. A hallmark of MS is that T cells infiltrate into the CNS. Higher numbers of IL-17 mRNA-expressing blood mono-nuclear cells (MNC) are detected during MS clinical exacerbation compared to remission (Multiple Sclerosis, 5:101-104, 1999). Furthermore, experimental autoimmune encephalomyelitis ("EAE"), a preclinical animal model for MS is significantly suppressed in IL-17 knockout mice.

In one embodiment, the invention provides a method for the treatment or prevention of a condition including, but not limited to, airway inflammation, ankylosing spondylitis, asthma, RA (including juvenile RA), osteoarthritis, bone erosion, intraperitoneal abscesses and adhesions, IBD, Crohn's disease, allograft rejection, psoriasis, psoriatic arthritis, certain types of cancer, angiogenesis, atherosclerosis and MS, as well as other inflammatory disorders, conditions, diseases or states including without limit: erythematosus, response to allergen exposure, *Helicobacter pylori* associated gastritis, bronchial asthma, allograft rejection (e.g., renal), systemic lupus erythematosus and lupus nephritis. The method comprises the step of administering to a subject in need thereof an amount of a compound or composition of the invention effective to treat the condition.

In another embodiment, the invention provides a method for the treatment or prevention of a condition including, but not limited to, Behcet's disease, ulcerative colitis, Wegener's granulomatosis, sarcoidosis, systemic sclerosis, insulin-dependent diabetes mellitus, septic shock syndrome, Alzheimer's disease, an inflammatory eye disease, and uveitis.

In a more specific embodiment, a compound of the invention or a pharmaceutical composition comprising a compound of the invention may be useful for the treatment or prevention of a condition selected from RA, airway inflammation, MS, psoriasis, psoriatic arthritis, and ankylosing spondylitis. More specifically, the condition is RA.

The use of the compounds of the present invention for treating or preventing of at least one of the aforementioned disorders in which IL-17 activity is detrimental or which benefits for decreased levels of bioactive IL-17 is contemplated herein. Additionally, the use of a compound of the present invention for use in the manufacture of a medicament for the treatment of at least one of the aforementioned disorders is contemplated.

In another aspect, the invention provides a method of treating a patient suffering from a disease or condition associated with elevated levels of IL-17 comprising the steps of: a) determining whether the patient has an elevated level of IL-17; and b) if the patient does have an elevated level of IL-17, administering to the patient an effective amount of a compound of Formula I for a time sufficient to treat the disease or condition.

In still another aspect, the invention provides a method of treating a patient suffering from a disease or condition associated with elevated levels of IL-17 comprising the steps of: a) determining whether the patient has an elevated level of one or more IL-17-induced chemokine or effector; and b) if the patient does have an elevated level of the one or more IL-17 chemokine or effector, administering to the patient an effective amount of a compound of Formula I for a time sufficient to treat the disease or condition. In certain aspects the IL-17 chemokine or effector is one or more of IL-6, IL-8, G-CSF, TNF-α, IL-1β, PGE2, and IFN-γ.

Methods for determining the levels of IL-17 or any of its chemokines or effectors in a patient are well-known in the art. Typically, a tissue or biological fluid sample is obtained from the patient and is subject to ELISA with commercially available antibodies or kits (e.g., Quantikine IL-17 ELISA; R&D Systems, Abington, UK). Commercially available antibodies and kits are available for IL-6, IL-8, G-CSF, TNF-α, IL-1β, PGE2, and IFN-γ.

The invention also provides for combination therapy of a macrocyclic compound described herein and a second therapeutic agent. "Combination therapy" (or "co-therapy") includes the administration of a macrocyclic compound described herein and at least a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected).

Combination therapy is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single dosage form having a fixed ratio of each therapeutic agent or in multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. Combination therapy also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (e.g., surgery or radiation treatment.) Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

Accordingly, in certain instances, the method further comprises administering a therapeutically effective amount of an anti-inflammatory agent. In certain instances, the anti-inflammatory agent is a salicylate, diclofenac, aceclofenac, acemetacin, alclofenac, bromfenac, etodolac, indometacin, nabumetone, oxametacin, proglumetacin, sulindac, tolmetin, piroxicam, droxicam, lornoxicam, meloxicam, tenoxicam, ibuprofen, alminoprofen, carprofen, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuproxam, indoprofen, ketorolac, loxoprofen, naproxen, oxaprozin, pirprofen, suprofen, tiaprofenic acid, mefenamic acid, flufenamic acid, meclofenamic acid, tolfenamic acid, phenylbutazone, ampyrone, azapropazone, clofezone, kebuzone, metamizole, mofebutazone, oxyphenbutazone, phenazone, phenylbutazone, sulfinpyrazone, celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib, prednisone, methylprednisolone, hydrocortisone, or budesonide.

In certain instances, the method further comprises administering a therapeutically effective amount of an agent for treating multiple sclerosis. In certain instances, the agent for treating multiple sclerosis is interferon beta-2, interferon beta-1, glatiramer, natalizumab, or mitoxantrone.

In certain instances, the method further comprises administering infliximab, etanercept, adalimumab, or certolizumab pegol.

In certain instances, the method is designed to treat rheumatoid arthritis and further comprises the step of administering to the patient in need thereof a therapeutically effective amount of an agent selected from the group consisting of a salicylate, diclofenac, aceclofenac, acemetacin, alclofenac, bromfenac, etodolac, indometacin, nabumetone, oxametacin, proglumetacin, sulindac, tolmetin, piroxicam, droxicam, lornoxicam, meloxicam, tenoxicam, ibuprofen, alminoprofen, carprofen, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuproxam, indoprofen, ketorolac, loxoprofen, naproxen, oxaprozin, pirprofen, suprofen, tiaprofenic acid, mefenamic acid, flufenamic acid, meclofenamic acid, tolfenamic acid, phenylbutazone, ampyrone, azapropazone, clofezone, kebuzone, metamizole, mofebutazone, phenazone, sulfinpyrazone, celecoxib, etoricoxib, lumiracoxib, parecoxib, prednisone, methylprednisolone, hydrocortisone, and budesonide.

IV. PHARMACEUTICAL COMPOSITIONS AND DOSING

The invention also provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the macrocyclic compounds of Formula I, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents, and optionally, one or more additional therapeutic agents described above. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, troches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, oral, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient will range from about 0.01 to about 50 mg per kilogram of body weight per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain aspects of the invention, dosing is one administration per day.

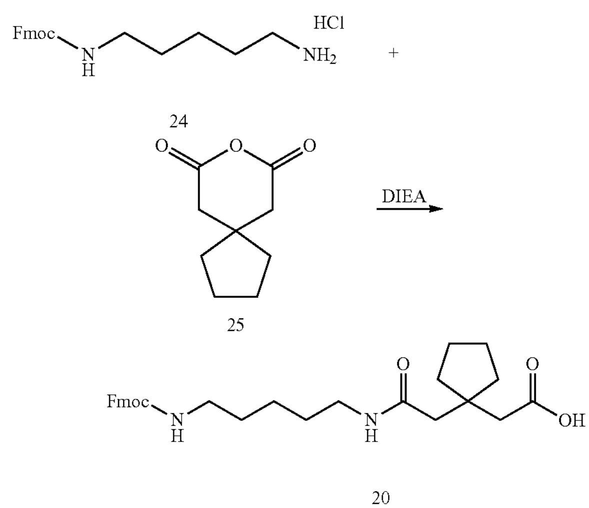
While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

EXAMPLES

The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1

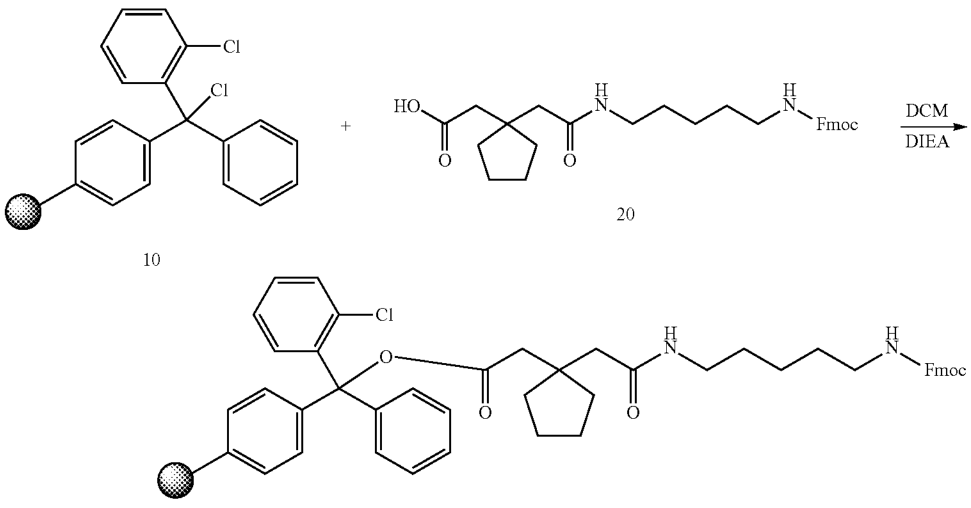
Synthesis of 2-(1-(2-(4-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-2-oxoethyl)cyclopentyl)acetic Acid (Intermediate 20)



(9H-fluoren-9-yl)methyl (5-aminopentyl)carbamate hydrochloride (24; 3.2 g, 8.9 mmol) and N-ethyl-N-isopropylpropan-2-amine (8.7 mL, 49.5 mmol) were dissolved in DMF (40 mL) followed by addition of 8-oxaspiro[4.5]decane-7,9-dione (25; 5 g, 29.7 mmol). The mixture was agitated for 1 hr followed by evaporation of volatiles. The crude product was purified directly on a Biotage purification system using 45%-75% acetonitrile/water. After evaporation of volatiles and lyophilization, a white powder was isolated consistent with desired product 20 (1.5 g, 3.0 mmol, 34%).

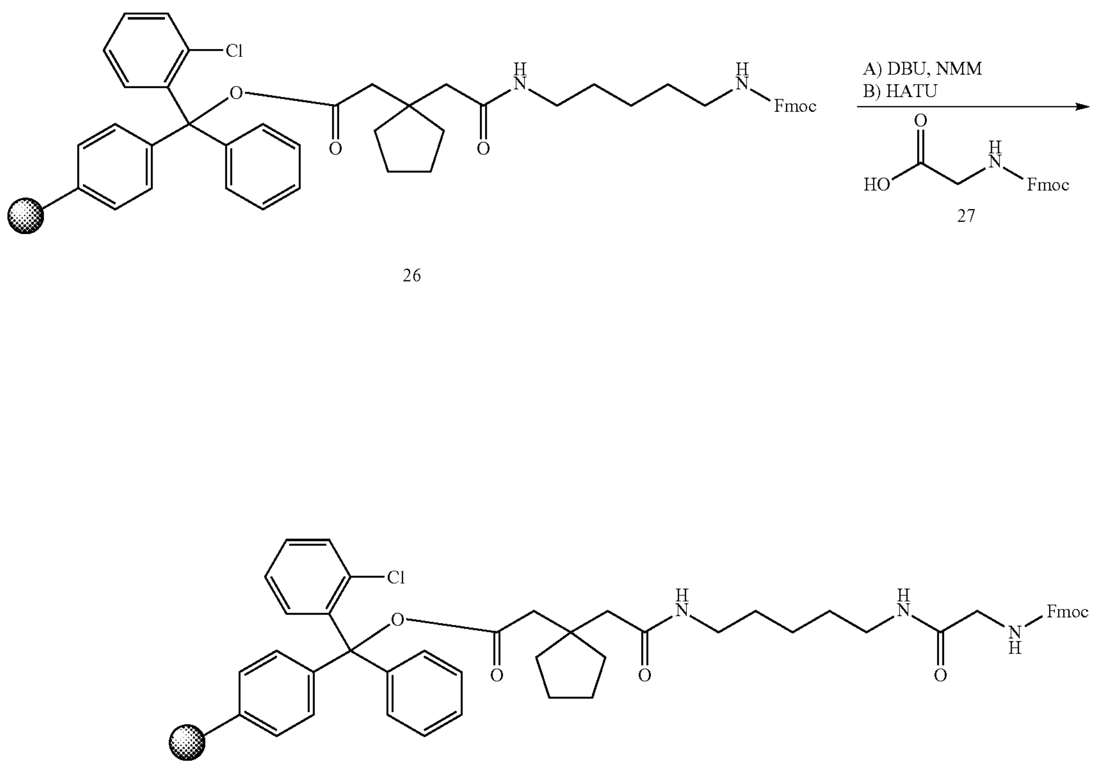
Example 2

Synthesis of Compound 159



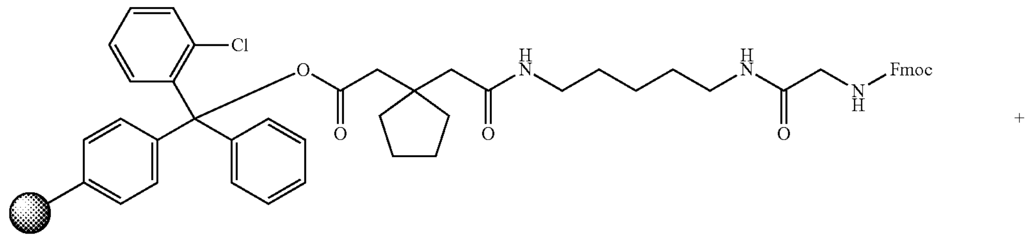
10 20 26

2-Chloro-trityl chloride resin (10; 0.58 g, 0.70 mmol) was swelled in DCM (5 mL) for 10 min, then filtered, and washed with DCM (5 mL). 2-(1-(2-(4-(((9H-fluoren-9-yl)methoxy) carbonylamino)butylamino)-2-oxoethyl)cyclopentyl)acetic acid (20; 0.335 g, 0.700 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.610 mL, 3.50 mmol) was dissolved in DCM (30 mL). The resulting solution was added to the swelled resin and agitated for 2 hours. The resin was then washed with 85:10:5 DCM:MeOH:DIPEA (5 mL×3); DCM (5 mL×3), DMF (5 mL×3), and DCM (5 mL×3). After flushing with argon and drying under vacuum, resin 26 (0.99 g) was obtained.

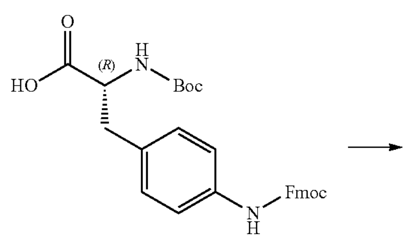


26 27 28

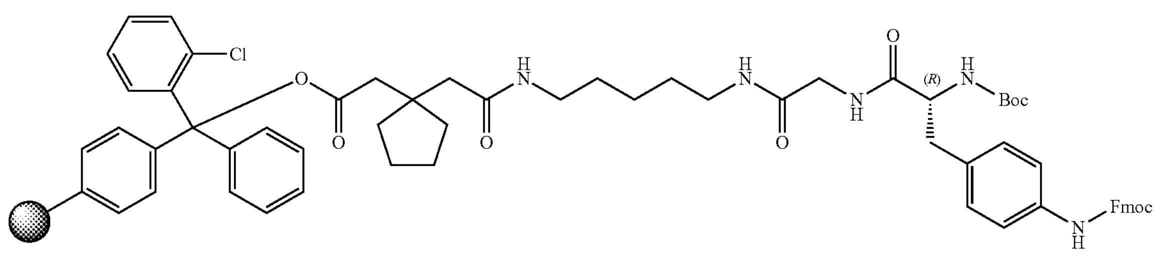
Resin 26 (0.075 mmol, 125 mg) was suspended in DMF (2 mL×5 min) and mixed with a stream of N_2 every 30 seconds. The Fmoc group was removed from the resin-supported building block by mixing the resin twice with a solution of 2% DBU, 2% piperidine in DMF (2 mL×5 min) while agitating with a stream of N_2 every 30 seconds. The resin was washed six times with DMF (2 mL×30 sec). Fmoc-glycine (27; 0.1 M solution in DMF, 2.5 mL, 3.3 equiv, 0.25 mmol), followed by HATU (0.2 M solution in DMF, 1.15 mL, 3.1 equiv, 0.23 mmol) and N-methyl morpholine (1.0 M in DMF, 0.5 mL, 6.7 equiv, 0.5 mmol) were added to the resin. The reaction mixture was agitated by a stream of nitrogen for 30 min. The reagents were drained from the reaction vessel, and the resin 28 was washed six times with DMF (2 mL×30 sec).



28

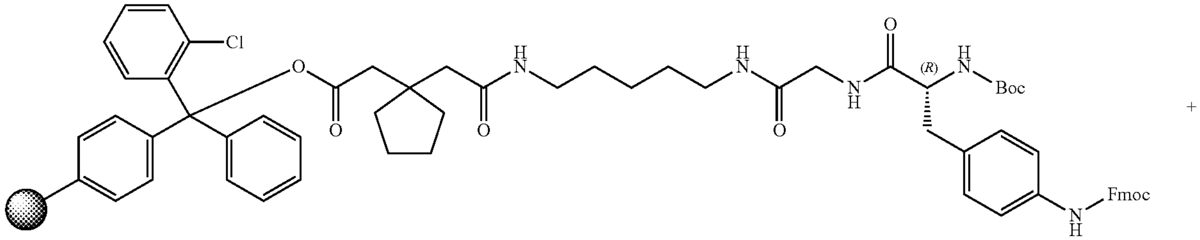


29

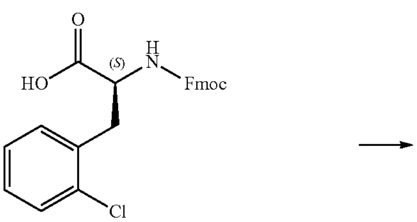


30

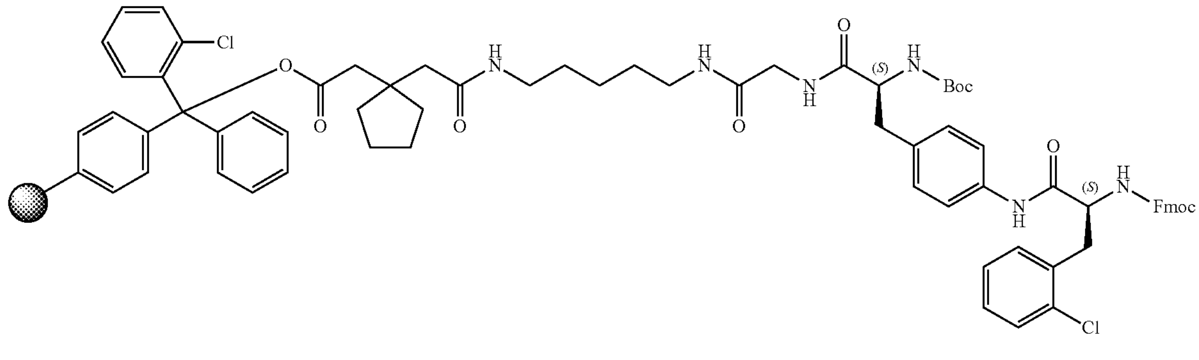
Resin 28 (0.075 mmol, 125 mg) was suspended in DMF (2 mL×5 min) and mixed with a stream of N_2 every 30 seconds. The Fmoc group was removed from the resin-supported building block by mixing the resin twice with a solution of 2% DBU, 2% piperidine in DMF (2 mL×5 min) while agitating with a stream of N_2 every 30 seconds. The resin was washed six times with DMF (2 mL×30 sec). (R)-3-(4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-phenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid 29; (0.1 M solution in DMF, 2.5 mL, 3.3 equiv, 0.25 mmol), followed by HATU (0.2M solution in DMF, 1.15 mL, 3.1 equiv, 0.23 mmol) and N-methyl morpholine (1.0 M in DMF, 0.5 mL, 6.7 equiv, 0.5 mmol) were added to the resin. The reaction mixture was agitated by a stream of nitrogen for 30 min. The reagents were drained from the reaction vessel, and the resin 30 was washed six times with DMF (2 mL×30 sec).



30

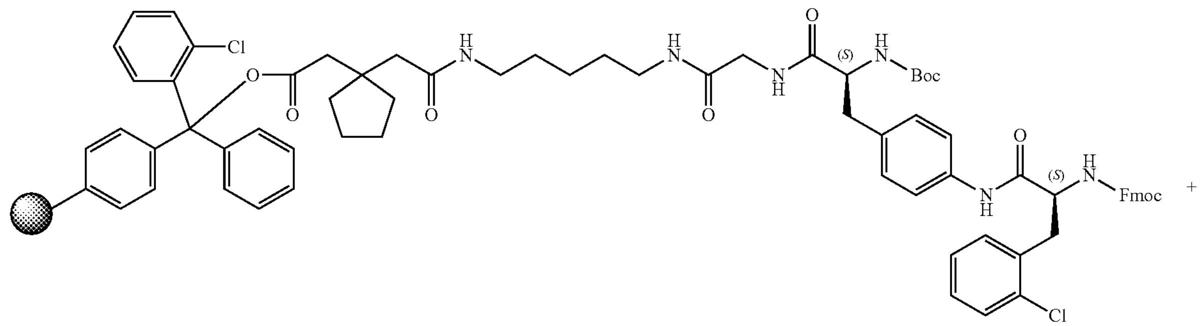


31

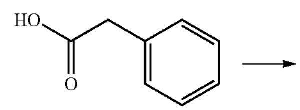


32

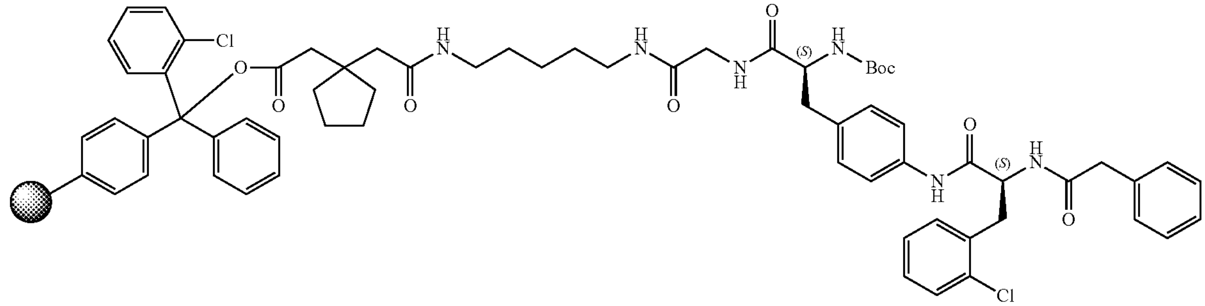
Resin 30 (0.075 mmol, 125 mg) was suspended in DMF (2 mL×5 min) and mixed with a stream of N_2 every 30 seconds. The Fmoc group was removed from the resin-supported building block by mixing the resin twice with a solution of 2% DBU, 2% piperidine in DMF (2 mL×5 min) while agitating with a stream of N_2 every 30 seconds. The resin was washed six times with DMF (2 mL×30 sec). Fmoc-2-chlorophenylalanine (31; 0.1 M solution in DMF, 2.5 mL, 3.3 equiv, 0.25 mmol), followed by HATU (0.2M solution in DMF, 1.15 mL, 3.1 equiv, 0.23 mmol) and N-methyl morpholine (1.0 M in DMF, 0.5 mL, 6.7 equiv, 0.5 mmol) were added to the resin. The reaction mixture was agitated by a stream of nitrogen for 5 hr. The reagents were drained from the reaction vessel, and the resin 32 was washed six times with DMF (2 mL×30 sec).



32

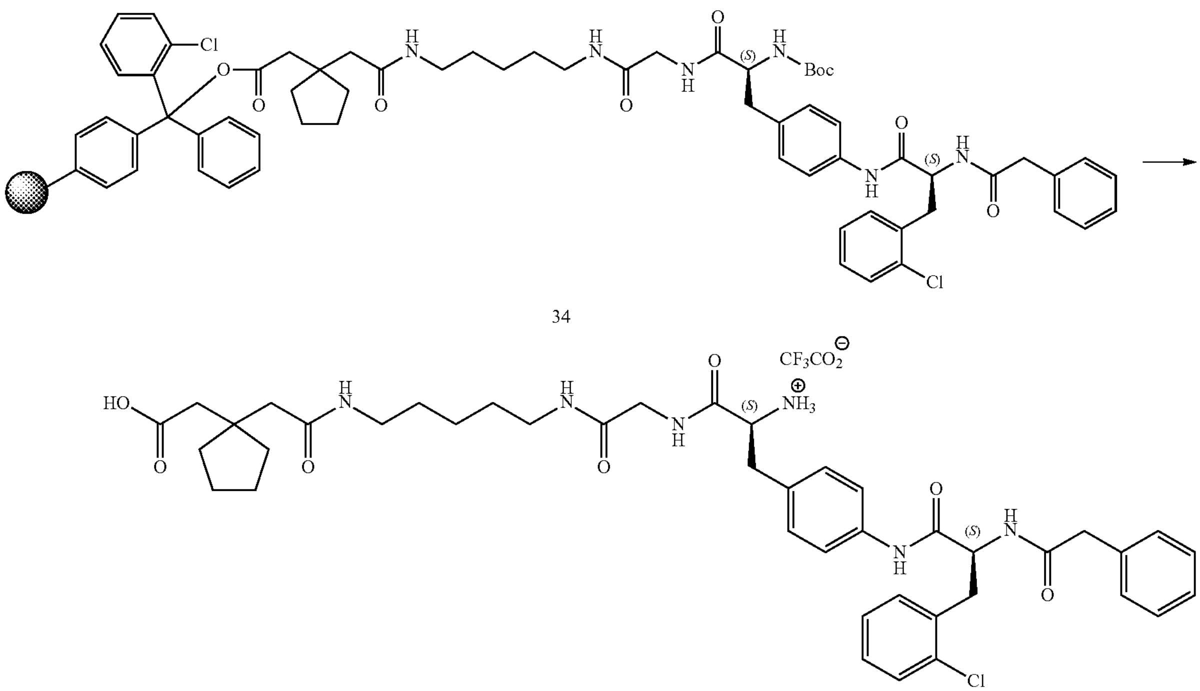


33



34

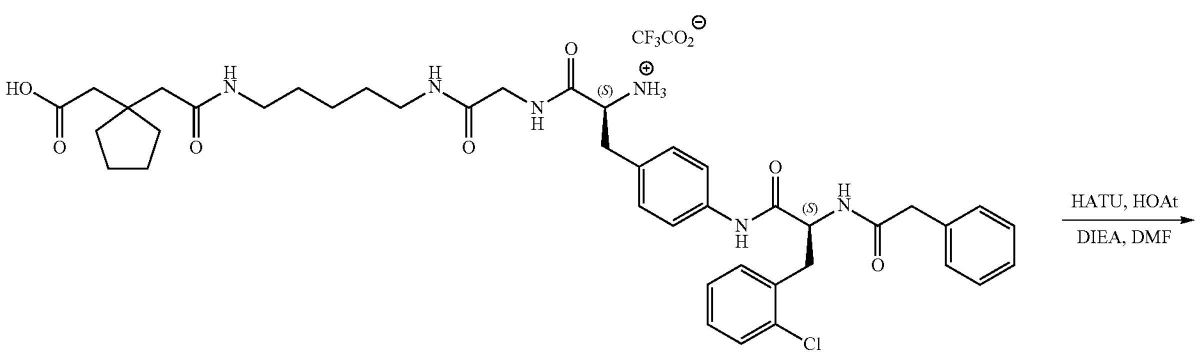
Resin 32 (0.075 mmol, 125 mg) was suspended in DMF (2 mL×5 min) and mixed with a stream of N_2 every 30 seconds. The Fmoc group was removed from the resin-supported building block by mixing the resin twice with a solution of 2% DBU, 2% piperidine in DMF (2 mL×5 min) while agitating with a stream of N_2 every 30 seconds. The resin was washed six times with DMF (2 mL×30 sec). Phenylacetic acid (33; 0.1M solution in DMF, 2.5 mL, 3.3 equiv, 0.25 mmol), followed by HATU (0.2M solution in DMF, 1.15 mL, 3.1 equiv, 0.23 mmol) and N-methyl morpholine (1.0 M in DMF, 0.5 mL, 6.7 equiv, 0.5 mmol) were added to the resin. The reaction mixture was agitated by a stream of nitrogen for 30 min. The reagents were drained from the reaction vessel, and the resin 34 was washed six times with DMF (2 mL×30 sec), and six times with DCM (2 mL×30 sec).



34

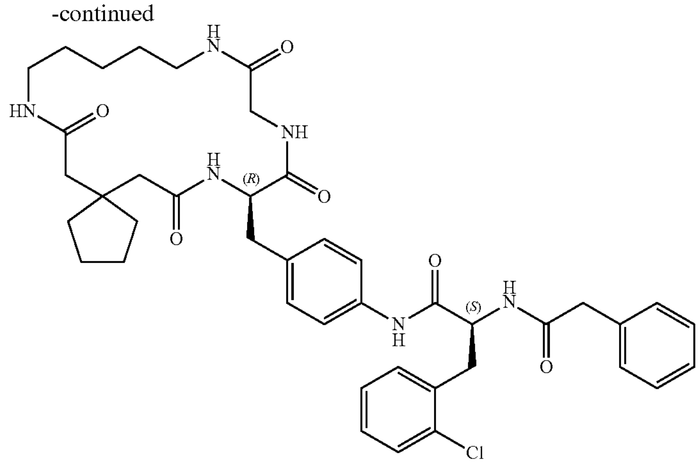
35

Resin 34 (0.075 mmol, 125 mg) was treated with 5% TFA in CH_2Cl_2 (4 mL×5 min) then washed with DCM (4 mL). Treatment with TFA was repeated two more times and the fractions combined. TFA (1 mL) was added and solvent was removed by evaporation using a Genevac EZ2.2 evaporator. The crude reaction mixture 35 was carried on to the next reaction.



35

-continued

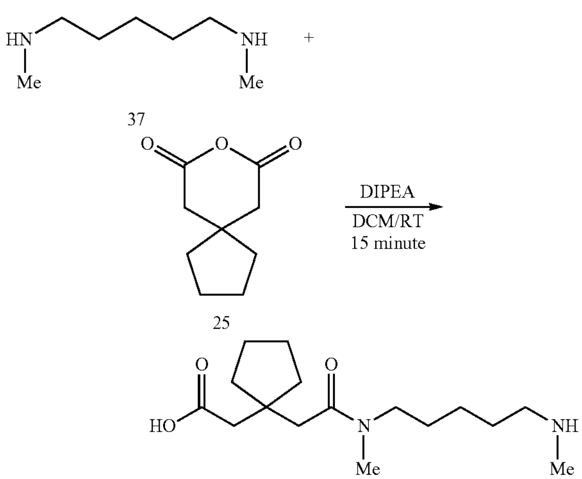


Compound 159

Crude reaction product 35 (0.075 mmol) and DIEA (0.13 mL, 10 equiv) were dissolved in DMF (5 mL). This solution was added to a solution containing HATU (34 mg, 0.090 mmol, 1.2 equiv) and HOAt (12 mg, 0.090 mmol, 1.2 equiv) dissolved in DMF (30 mL). After 30 minutes, the volatiles were evaporated on a Genevac EZ2.2 evaporator at 50° C. The resultant crude mixture was dissolved in DMSO and purified on a Waters HPLC. Evaporation of volatiles followed by lyophilization resulted in Compound 159 (32 mg, 0.042 mmol, 56% yield) as a white powder.

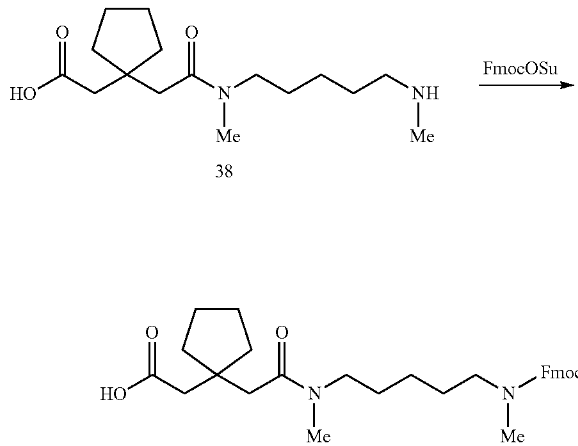
Example 3

Synthesis of 2-(1-(2-((5-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pentyl)(methyl)amino)-2-oxoethyl)cyclopentyl)acetic Acid (Intermediate 39)



38

A 250 mL flask with magnetic stirring bar is charged with 1,5-di(methylamino)pentane (37; 1.0 g, 7.7 mmol), followed by 120 mL of dichloromethane. The mixture is stirred at room temperature for 5 minutes followed by addition of 8-oxazpiro [4.5]decane-7,9-dione (25; 1.29 g, 7.7 mmol) and diisopropylethylamine (1.34 mL, 30.8 mmol). The solution is allowed to stir for 15 minutes and the resulting 2-(1-(2-(methyl(5-(methylamino)pentyl)amino)-2-oxoethyl)cyclopentyl)acetic acid 38 is used directly for the next reaction without any purification.



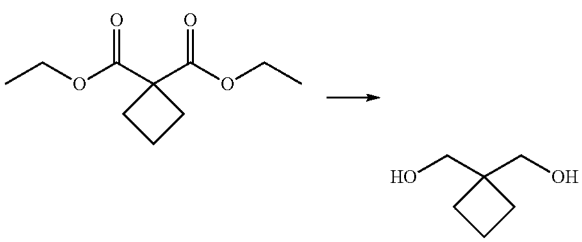
39

To the above solution is introduced (9H-fluoren-9-yl)methyl (2,5-dioxopyrrolidin-1-yl) carbonate (3.1 g, 9.2 mmol). The solution is stirred for 15 minutes. The resulting mixture is treated with 1.2N HCl solution and the pH adjusted to 3.0. The organic layer is separated and dried with Na_2SO_4. The crude product is purified by silica gel chromatography (acetonitrile/methylene chloride: 0-30%) providing a white powder (1.8 g, 3.4 mmol, 45% from diamine) consistent with desired product 39. The desired product 39 can be utilized in general Scheme 1 as a version of intermediate 11, or in general Scheme 2, as a version of intermediate 15.

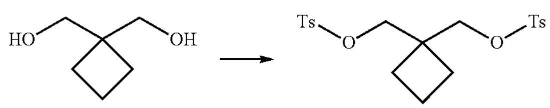
Other compounds of Formula I were made by a similar process as described above with the appropriate substitution for one or more of reagents 20, 24, 25, 27, 29, 31, 33 and/or 37. Those of ordinary skill in the art should make reference to Schemes 1-4 herein, commercially available reagents/compounds and standard organic chemistry protocols to obtain appropriate substitutions for any of these reagents.

Example 4

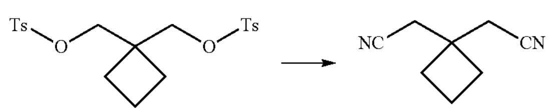
Synthesis of 7-oxaspir[3.5]nonane-6,8-dione



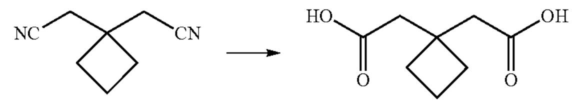
A solution of diethyl cyclobutane-1,1-dicarboxylate (4.76 ml, 24.97 mmol) in diethyl ether was cooled to 0° C. Aluminum(III) lithium hydride (49.9 ml, 100 mmol) in THF was added over 15 min. The reaction was warmed to room temperature and left to stir for 3 hours. A 20% solution of sodium hydroxide was added followed by diethyl ether. The organic layer was isolated, dried with magnesium sulfate, and concentrated under vacuum. Recovered cyclobutane-1,1-diyldimethanol (23.86 mmol, 96% yield) as pure material.



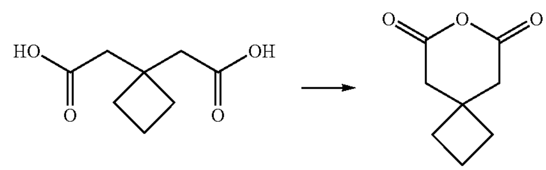
4-methylbenzene-1-sulfonyl chloride (13.79 g, 72.3 mmol) was dissolved in pyridine and cooled to 0° C. Cyclobutane-1,1-diyldimethanol (2.8 g, 24.11 mmol) in pyridine was added over 10 min. The mixture was stirred for 2 hours at 0° C. and then for 48 h at room temperature. The material was partitioned between 50 ml DCM and 50 ml water. The aqueous layer was washed with 1× with 50 ml DCM. The organic layers were combined and washed with 50 ml 1.2 M HCl and brine and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The material was then purified on Companion Combiflash using a gradient of 0-10% ethyl acetate in hexanes. The desired fractions were combined and dried down to give a white solid. Solvents were removed under reduced pressure to give cyclobutane-1,1-diylbis(methylene)bis(4-methylbenzenesulfonate) (8.72 mmol, 36.2% yield).



Cyclobutane-1,1-diylbis(methylene)bis(4-methylbenzenesulfonate) (3.7 g, 8.72 mmol) was dissolved in 5 ml DMSO. KCN (1.703 g) was added and the mixture stirred overnight at 90° C. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (50 ml×3). The organic extracts were combined, washed with brine (50 ml), dried over $MgSO_4$, and concentrated under vacuum to give 2,2'-(cyclobutane-1,1-diyl)diacetonitrile (8.71 mmol, 100% yield).



2,2'-(cyclobutane-1,1-diyl)diacetonitrile (1.169 g, 8.71 mmol) was dissolved in 20% KOH, heated to reflux and refluxed for 48 h. Concentrated HCl was added dropwise until solution reached a pH of 1 and the solution was extracted with DCM (3×10 ml). Organic layers were combined and dried over $MgSO_4$, filtered, and concentrated to give 2,2'-(cyclobutane-1,1-diyl)diacetic acid (4.07 mmol, 46.7% yield).

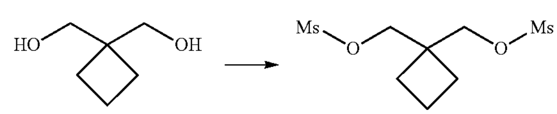


2,2'-(cyclobutane-1,1-diyl)diacetic acid (0.7 g, 4.07 mmol) was dissolved in acetic anhydride (5.75 mL, 61.0 mmol) and refluxed overnight. The solution was cooled to r.t. Acetic anhydride was removed under reduced pressure to give a brown oil, which was then recrystallized by dissolving in ether/hexanes, cooling to 0° C. and collecting crystals by vacuum filtration. The crystals were dried under vacuum overnight producing 7-oxaspiro[3.5]nonane-6,8-dione (2.147 mmol, 52.8% yield) as a light brown solid.

The resulting 7-oxaspiro[3.5]nonane-6,8-dione was used as intermediate 9 in Schemes 4A and 4B set forth previously to produce compounds of the invention having a cyclobutyl glutarate moiety (e.g, Compound Nos. 535 and 536).

Example 5

Synthesis of cyclopropane-1,1-diylbis(methylene) dimethanesulfonate



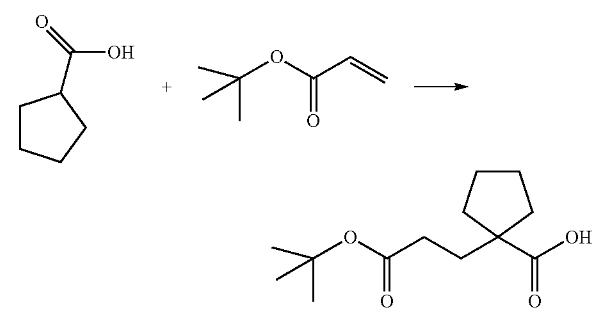
Cyclopropane-1,1-diyldimethanol (0.5 g, 4.90 mmol) was dissolved in DCM (6 ml). Triethylamine (2.73 mL, 19.58 mmol) was added, as was a solution of methanesulfonyl chloride (1.141 mL, 14.69 mmol) in DCM (4 ml) at 0° C. The mixture was stirred for 2 h at room temperature. After 2 h, 1.2N HCl was added, and the aqueous layer removed and washed 3× with DCM. The resulting organic layers were combined with the original layer, dried over $MgSO_4$, filtered, and concentrated to give 1.31 g crude material. The crude material was washed with hexanes to produce cyclopropane-1,1-diylbis(methylene)dimethanesulfonate (2.323 mmol, 47.4% yield).

The resulting cyclopropane-1,1-diylbis(methylene) dimethanesulfonate was used in place of cyclobutane-1,1-diylbis(methylene)bis(4-methylbenzenesulfonate) in Example 4 and, following the procedures set forth in Example 4, ultimately produced 6-oxaspiro[2.5]octane-5,7-dione.

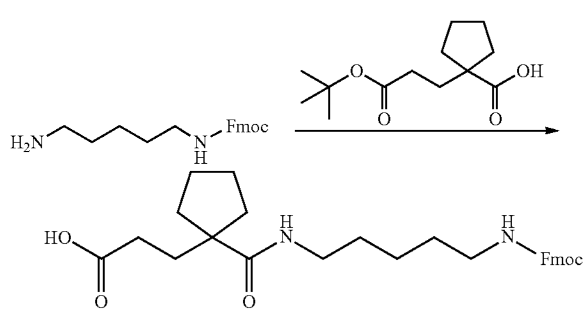
6-oxaspiro[2.5]octane-5,7-dione was used as intermediate 9 in Schemes 4A and 4B set forth previously to produce compounds of the invention having a cyclopropyl glutarate moiety (e.g., Compound No. 554).

Example 6

Synthesis of 3-(1-(5-(((9H-fluoren-9-yl)methoxy) carbonylamino)pentylcarbamoyl)cyclopentyl)propano ic Acid

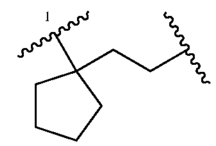


To a 50 ml round-bottomed flask under nitrogen was added lithium diisopropylamide (10.95 mL, 21.90 mmol). The solution was cooled to −20° using a controlled dry ice/acetonitrile bath. Cyclopentanecarboxylic acid (1.187 mL, 10.95 mmol) in dry THF (10 mL) was added over 5 minutes, keeping the temperature at −20° C. The mixture was warmed to room temperature, stirred for one hour, then cooled to −78° C. Tert-butyl acrylate (1.685 mL, 10.95 mmol) in dry THF (10 mL) was added dropwise over 5 min, keeping the temperature at −70° C. After 2 hours at −70° C., the mixture was quickly warmed to 0° C., acidified with 5N HCl, and extracted with hexane. The hexane extract was washed with water and saturated sodium bicarbonate, water, and dried over $MgSO_4$, and then recrystallized from hexanes. Recovered 1-(3-tert-butoxy-3-oxopropyl)cyclopentanecarboxylic acid (1.8 g, 7.43 mmol, 67.8% yield).



To a solution of (9H-fluoren-9-yl)methyl 5-aminopentylcarbamate (0.683 g, 2.105 mmol) in 15 ml DMF was added HATU (0.800 g, 2.105 mmol), 1-(3-tert-butoxy-3-oxopropyl) cyclopentanecarboxylic acid (0.425 g, 1.754 mmol) in 5 ml DMF, and DIEA (1.532 mL, 8.77 mmol). The solution was stirred for 10 minutes and material purified by HPLC using a gradient of 0-50% acetonitrile in DCM. Solvents were removed under reduced pressure to give 1.2 g crude tert-butyl 3-(1-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)-pentylcarbamoyl)cyclopentyl)propanoate. The crude material was dissolved in 20 ml DCM and 10 ml TFA was added to remove t-Bu group. Solvent was removed under reduced pressure and material purified by reverse phase chromatography to give 3-(1-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylcarbamoyl)cyclopentyl)propanoic acid (16 mg, 0.032 mmol, 1.852% yield).

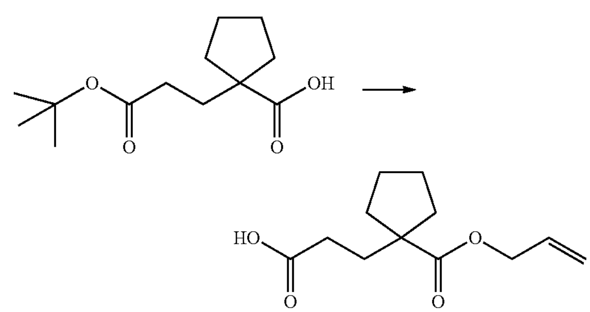
The resulting 3-(1-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylcarbamoyl)cyclopentyl)propanoic acid was employed as intermediate 15 in Scheme 2 to produce compounds of the invention where R^3 is



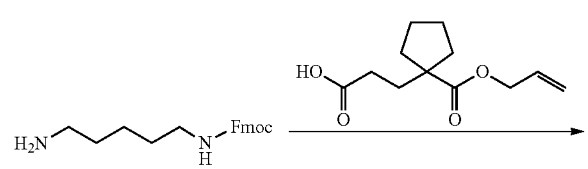
e.g. (Compound 543).

Example 7

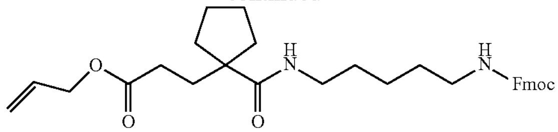
Synthesis of 1-(3-(5-(((9H-fluoren-9-yl)methoxy) carbonylamino)pentylamino)-3-oxopropyl)cyclopentane Carboxylic Acid



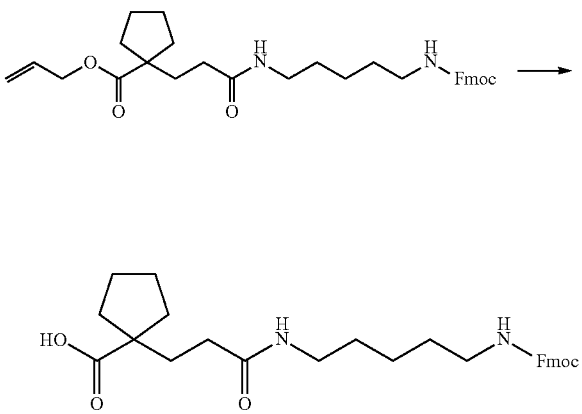
1-(3-tert-butoxy-3-oxopropyl)cyclopentanecarboxylic acid (1.275 g, 5.26 mmol) and 3-bromoprop-1-ene (0.911 mL, 10.52 mmol) were dissolved in 25 mL of acetone. Potassium carbonate (2.55 g, 18.42 mmol) was then added in one portion. The resulting suspension was stirred at reflux for 3 hours. The insoluble inorganic salts were removed by filtration and the reaction mixture was concentrated under reduced pressure to yield crude product. The crude product was dissolved in dichloromethane (10 mL) to which was added TFA (2.5 ml) to remove Boc group. The reaction was stirred for 15 min then the solvent removed under reduced pressure to give crude material (1.04 g, quantitative yield), which was used without further purification.



-continued

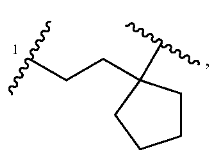


To a solution of 3-(1-(allyloxycarbonyl)cyclopentyl)propanoic acid (1.191 g, 5.26 mmol) in 40 ml DMF was added (9H-fluoren-9-yl)methyl 5-aminopentylcarbamate (2.049 g, 6.32 mmol), DIEA (4.60 mL, 26.3 mmol) and HATU (2.402 g, 6.32 mmol). After stirring for 10 minutes, DMF was removed under reduced pressure. The material was subjected to normal-phase purification using a gradient of 0-100% acetonitrile in DCM. Fractions containing the desired material were combined and solvent removed under reduced pressure to give crude allyl 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentanecarboxylate (360 mg, 0.676 mmol, 12.84% yield) that was used in the next step without further purification.



Allyl 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentanecarboxylate (360 mg, 0.676 mmol) was dissolved in DMF (15 mL) and cooled to 0° C. under nitrogen. Tetratritylpalladium (122 mg, 0.113 mmol) and morpholine (941 mg, 10.8 mmol) were added and the mixture stirred for 2 h. Solvent was removed under reduced pressure and material was purified by reverse-phase chromatography. Recovered 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentanecarboxylic acid (54.4 mg, 0.110 mmol, 16.34% yield).

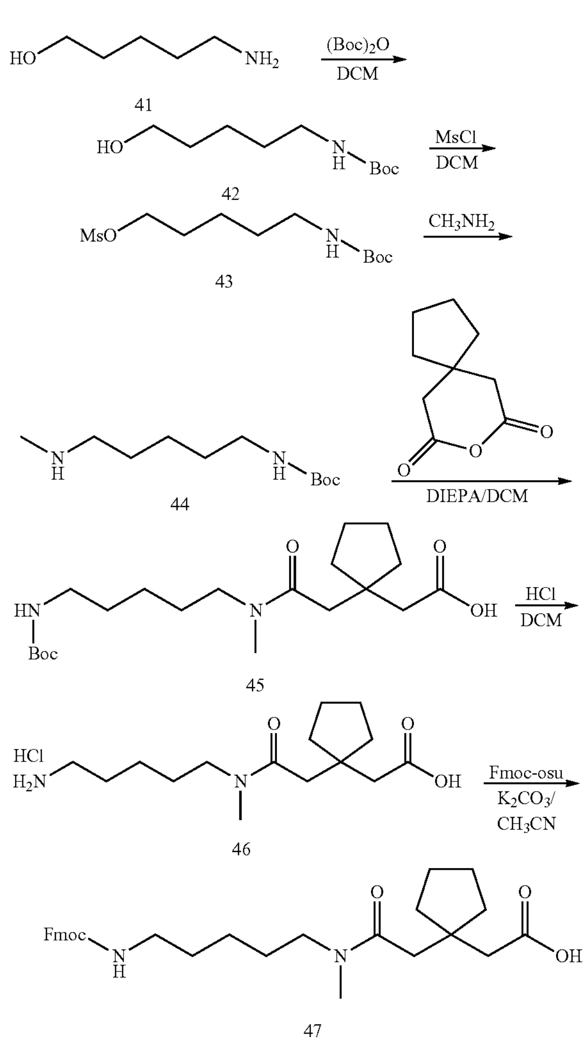
The resulting 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentanecarboxylic acid was employed as intermediate 15 in Scheme 2 to produce compounds of the invention where R^3 is



e.g., Compound 561.

Example 8

Synthesis of 2-(1-(2-((5-(((9H-fluoren-9-yl)methoxy)carbonyl)pentyl)(methyl)amino)-2-oxoethyl)cyclopentyl)acetic Acid (47)



To a solution of 41 (20 g, 194 mmol) in DCM (0.2 L) was added $(Boc)_2O$ dropwise (42.3 g, 194 mmol) under an ice bath. The reaction was stirred at RT over night. Then the mixture solution was extracted with DCM and washed with water. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The solvent was removed in vacuum to give 42 as an oil (37 g, yield 93.1%). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.5 (m, 2H), 3.2 (m, 2H), 1.6-1.5 (m, 4H), 1.4-1.3 (m, 11H).

To a solution of 42 (10 g, 49.2 mmol) in DCM (100 mL) and Et_3N (9.9 g, 98.5 mmol) was added methanesulfonyl chloride (6.7 g, 59.1 mmol) in portions over 20 minutes under an ice bath. The reaction was stirred for 1 hour. The mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give 43 (12 g, yield: 86.9%). ^1H NMR (300 MHz, $CDCl_3$) δ: 4.0 (m, 2H), 3.1-3.0 (m, 3H), 3.2-3.1 (m, 2H), 1.6-1.5 (m, 4H), 1.4-1.3 (m, 11H).

To a solution of 43 (12 g, 42 mmol) in 1,4-dioxane (100 mL) was added CH_3NH_2 aqueous slowly (30%, 100 ml) at 60° C. The mixture was stirred at 60° C. for 1 h. The reaction was concentrated and purified by a silica gel column (eluting with 3% Et_3N/THF) to give 44 (5.2 g, yield 56.5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.2-3.1 (s, 2H) 2.9-2.9 (m, 3H), 2.6-2.5 (m, 2H), 1.6-1.5 (s, 2H), 1.4-1.3 (s, 11H).

To a solution of 44 (3.2 g, 14.8 mmol) was added 8-oxaspiro[4.5]decane-7,9-dione (2.9 g, 17.7 mmol) in DCM (30 mL). The resulting mixture was stirred at RT for 1 h. Then, the mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-30% EA/PE, 2% AcOH) to give 45 (3.5 g, yield 62.5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.5-3.4 (m, 2H), 3.3 (m, 2H), 3.1 (m, 2H), 3.0 (m, 1H), 2.5 (m, 4H), 1.8-1.4 (s, 25H).

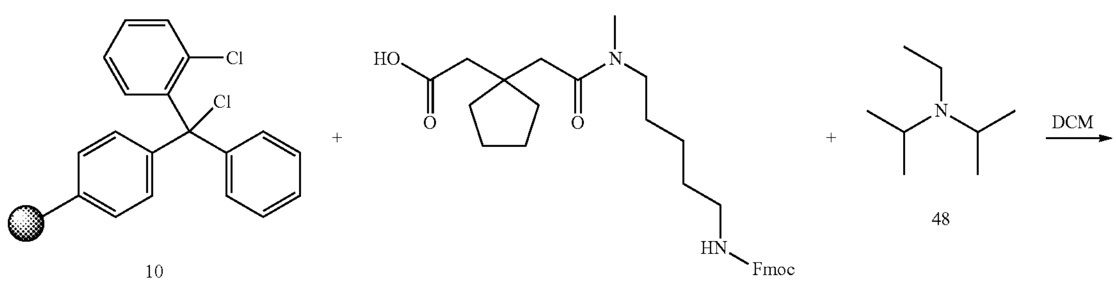
To a solution of 45 (3.5 g, 9.1 mmol) in 40 mL DCM was added Et_2O/HCl slowly (4 mol/L, 40 ml) under ice bath. Then, the mixture was stirred at room temperature overnight. The mixture was concentrated and washed with Et_2O to give 46 (2.2 g, yield 75.8%). ^{1}H NMR (300 MHz, DMSO) δ: 3.5-3.4 (m, 2H), 3.3 (m, 2H), 3.1 (m, 2H), 3.0 (m, 1H), 2.5 (m, 4H), 1.8-1.4 (s, 16H).

To a solution of 46 (2.2 g, 6.8 mmol) and potassium carbonate (1.9 g, 13.7 mmol) in acetonitrile (20 mL) and water (40 mL) was added Fmoc-osu (2.5 g, 7.5 mmol) in acetonitrile (20 mL) over 10 minutes under an ice bath. The mixture was stirred under ice bath for about 1 h. Then, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-30% EA/PE, 2% AcOH) to give 47 (2 g, yield 58.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.9-7.8 (d, 2H), 7.7-7.6 (d, 2H), 7.6-7.5 (d, 2H), 7.4-7.3 (m, 2H), 7.3-7.2 (d, 2H), 4.5-4.4 (m, 2H), 4.2 (m, 1H), 3.5-3.4 (m, 2H), 3.2 (m, 2H), 3.1 (m, 2H), 3.0 (m, 1H), 2.6-2.5 (m, 4H), 1.8-1.4 (s, 12H), 1.4-1.2 (s, 2H). LC-MS: m/z=529.2 $(M+23)^+$.

The resulting product 47 was employed as intermediate 15 in Scheme 2 to produce compounds of the invention, such as Compound 421. Alternatively, the resulting product was employed as intermediate 11 in Scheme 1 to produce compounds wherein R^1 is —$N(CH_3)$— and R^2 is —$(CH_2)_5$—N(H)—C(O)—C(H)(R^{11})—$(CH_2)_{0-2}$—. For other compounds of the invention, the resulting product was used as set forth in Example 9, below.

Example 9

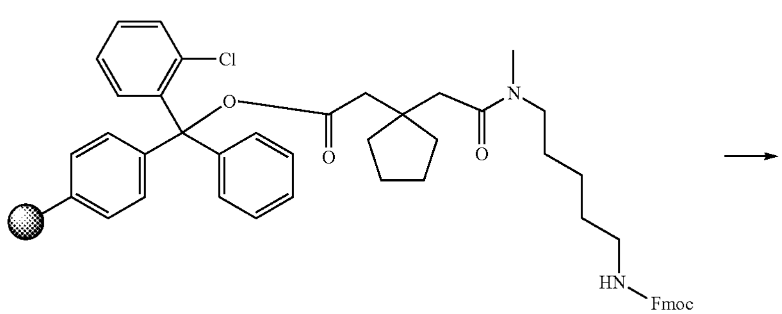
Synthesis of Resin-Linked Intermediate 51



10

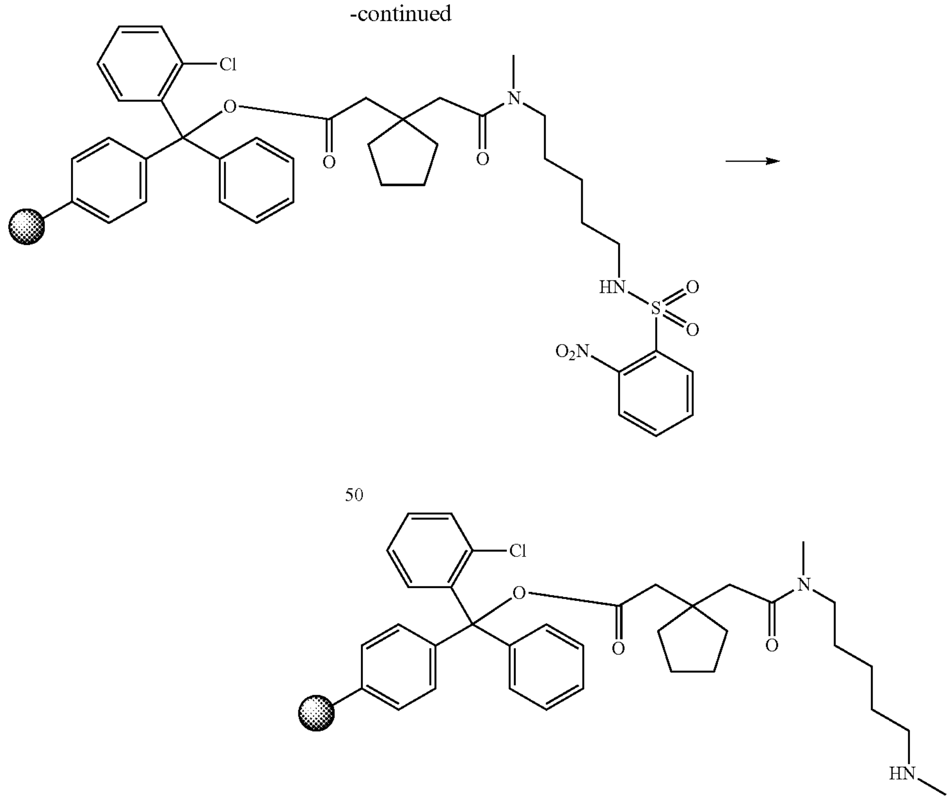
47

48



49

-continued



51

2-Chlorotrityl chloride resin (10; 0.658 g, 0.790 mmol) was added to a 20 mL plastic column. The resin was swelled with 10 mL anhydrous DCM and let sit for 20 minutes. The DCM was drained and the resin washed with 10 mL of DCM. 2-(1-(2-((5-(((9H-Fluoren-9-yl)methoxy)carbonylamino) pentyl)(methyl)amino)-2-oxoethyl)cyclopentyl)acetic acid (47; 0.400 g, 0.790 mmol) and N-ethyl-N-isopropylpropan-2-amine (48; 0.688 mL, 3.95 mmol) were dissolved in DCM (30 mL) in a 10 mL vial. The solution was loaded onto column containing the resin and rocked overnight. The solution was drained from the column, which was then washed with 85:10:5 DCM:MeOH:DIPEA (10 mL×2) and DCM (10 mL×3), and dried under light vacuum to produce resin 49. Resin loading was measured to be 0.3 mmol/g.

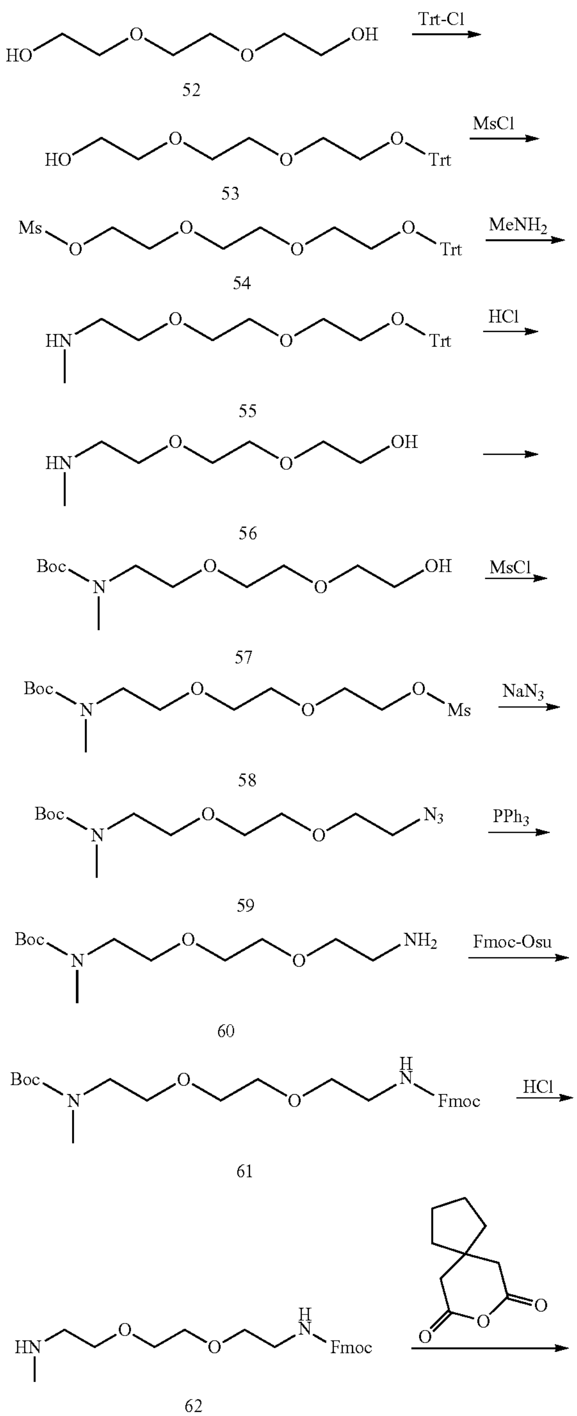
850 mg of resin 49 from the previous step was swelled in DMF (8 ml) for 15 min. The DMF was drained and 8 ml of 2% piperidine/2% DBU in DMF was added. After rotation for 5 min, the solution was drained and the resin washed 1× with DMF. 8 ml of 2% piperidine/2% DMF in DMF was added to the resin and rotated for 15 min. The solution was drained and the resin washed 5× with DMF. In a separate vial, 2-nitrobenzenesulfonyl chloride (0.222 g, 1.000 mmol) was dissolved in DMF (8 mL). To that was added 2,4,6-Collidine (0.330 mL, 2.500 mmol) and the mixture was vortexed. The NBS/collidine solution was added to the resin and rotated for 15 min. After draining the resin was washed 1× with DMF, and the treatment with NBS/collidine was repeated. The resulting resin 50 was washed 5× with DMF.

The resin 50 from the previous step was rinsed 2× with THF. In a vial, triphenylphosphine (0.328 g, 1.250 mmol) was dissolved in DMF (5 mL), MeOH (0.101 mL, 2.500 mmol) added, and the solution mixed well. The solution was added to the resin and rotated vigorously for 2 min. Diisopropyl azodicarboxylate (0.246 mL, 1.250 mmol) dissolved in THF (1 mL) was added to the resin in 200 μL portions and rocked for 10 min between each addition. The resin was then rocked overnight. The solution was drained from resin and resin was washed with THF (5×5 mL) followed by DCM (3×5 mL). The additions of triphenylphosphine and diisopropyl azodicarboxylate were repeated and the resin rocked for an additional 8 hours. In a separate vial, 2-mercaptoethanol (0.176 mL, 2.500 mmol) was dissolved in DMF (5 mL) and then DBU (0.188 mL, 1.250 mmol) was added. This solution was added to the resin and rotated for 5 min. The reaction solution was drained from the resin and the resin washed with DMF (2×5 ml). The resulting resin 51 was then washed thoroughly with DMF, followed by DCM.

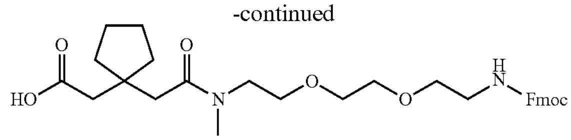
For certain compounds of the invention, the resulting resin 51 was used as resin 12 in general Scheme 1. For other compounds of the invention, the resulting resin 51 was used as resin 16 in general Scheme 2, e.g., Compounds 387, 488, 489, 524, 525, 566, 570, 600, 601, 602, 623, 625, 626, 627, 628, 629, 630, 631, 644, 645, 646, 653, 665, 669, and 670.

Example 10

Synthesis of 2-(1-(1-(9H-fluoren-9-yl)-13-methyl-3,14-dioxo-2,7,10-trioxa-4,13-diazapentadecan-15-yl)cyclopentyl)acetic Acid (63)



-continued



63

To a solution of 2,2'-(ethane-1,2-diylbis(oxy))diethanol (52; 100 g, 667 mmol) and Et_3N (18.5 mL, 133 mmol) in DCM (500 mL) was added triphenylmethyl chloride (abbreviated as (Trt-Cl) (18.6 g, 66.7 mmol) in DCM (10 mL) over 20 minutes under an ice bath. The progress of the reaction was checked by TLC. The solution was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 5-15% EA/PE, 1% Et_3N) to provide 53 (15 g, yield: 57.3%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.6-7.4 (m, 5H), 7.4-7.2 (m, 10H), 3.8-3.6 (m, 6H), 3.6-3.5 (m, 2H), 3.3-3.1 (m, 2H), 2.5-2.3 (s, 1H).

To a solution of 53 (15 g, 38.2 mmol) in DCM (100 mL) and Et_3N (8 mL, 45.9 mmol) was added methanesulfonyl chloride (5.2 g, 45.9 mmol) in portions over 10 minutes under an ice bath. The reaction was stirred for 1 hour. The mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give 54 (17 g, yield: 94.7%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.6-7.4 (m, 5H), 7.4-7.2 (m, 10H), 4.5-4.3 (m, 2H), 3.9-3.8 (m, 2H), 3.8-3.6 (m, 6H), 3.0 (s, 3H).

To a solution of 54 (17 g, 36 mmol) in THF (20 mL) was added CH_3NH_2 aqueous solution slowly (30%, 80 ml) at 60° C. The mixture was stirred at 60° C. for 4 h. The mixture was concentrated to provide 55 (14.5 g, yield: 99.8%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.7-7.4 (m, 7H), 7.4-7.2 (m, 8H), 3.9-3.7 (m, 8H), 3.3-3.2 (m, 2H), 2.8-2.8 (m, 2H), 2.5-2.4 (s, 3H).

To a solution of 55 (4.5 g, 36.1 mmol) in 30 mL DCM was added Et_2O/HCl (5.2 mol/L, 50 mL) at room temperature. Then, the mixture was stirred at room temperature over night. The mixture was filtered and the residue was washed with Et_2O to give 56 (7.2 g, yield: 99.6%).

To a solution of 56 (7.2 g, 36.1 mmol) in DCM (0.2 L) was added $(Boc)_2O$ dropwise (42.3 g, 194 mmol) under ice bath. The reaction was stirred at RT overnight. Then the mixture solution was extracted with DCM and washed with water. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The solvent was removed in vacuum and purified by a silica gel column (eluting with 20-50% EA/PE) to provide 57 (7 g, yield: 73.7%). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.8-3.6 (m, 11H), 3.5-3.3 (m, 2H), 3-2.8 (s, 3H), 1.6-1.5 (s, 9H).

To a solution of 57 (7 g, 26.6 mmol) in DCM (100 mL) and Et_3N (5.5 mL, 40 mmol) was added methanesulfonyl chloride (3.6 g, 32 mmol) in portions over 10 minutes under ice bath. The reaction was stirred for 1 hour. The mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give 58 (8 g, yield: 89.4%). ^1H NMR (300 MHz, $CDCl_3$) δ: 4.5-4.3 (m, 2H), 3.9-3.7 (m, 2H), 3.7-3.5 (m, 6H), 3.5-3.3 (s, 2H), 3.1 (s, 3H), 3-2.8 (s, 3H), 1.6-1.5 (s, 9H).

To a solution of 58 (8 g, 30.4 mmol) in DMF (0.1 L) was added sodium azide (3.2 g, 49.7 mmol) under an ice bath. The reaction was stirred ice bath for 4 h, H_2O (5 mL) was added and the mixture was stirred at room temperature for overnight. Then, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The solvent was removed in vacuum to provide 59 (7 g, yield: 79.9%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.8-3.5 (m, 6H), 3.5-3.4 (m, 2H), 3.1-2.8 (m, 5H), 1.6-1.5 (s, 9H).

To a solution of 59 (7.0 g, 24.3 mmol) in THF (50 mL) was added PPh_3 (7.6 g, 29.1 mmol) under an ice bath. The reaction was stirred ice bath for 4 h, H_2O (5 mL) was added and the mixture was stirred at room temperature for overnight. Then, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The solvent was removed in vacuum to provide 60 (5.6 g, yield: 62.3%).

To a solution of 60 (5.6 g, 21.4 mmol) and potassium carbonate (4.4 g, 32 mmol) in acetonitrile (25 mL) and water (25 mL) was added Fmoc-Osu (7.9 g, 23.5 mmol) in acetonitrile (25 mL) over 10 minutes under ice bath. The mixture was stirred for 30 minutes. After TLC, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 50/90% EA, 10% MeOH) to provide 61 (9.5 g, yield: 91.7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.8-7.7 (d, 2H), 7.7-7.6 (d, 2H), 7.5-7.3 (m, 4H), 4.6-4.4 (m, 2H), 4.4-4.3 (m, 1H), 3.8-3.5 (m, 7H), 3.5-3.2 (m, 4H), 3.0-2.8 (s, 3H), 1.6-1.5 (s, 9H).

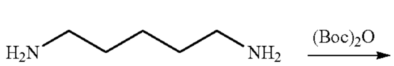
To a solution of 61 (9.5 g, 19.6 mmol) in 30 mL DCM was added Et_2O/HCl (5.2 mol/L, 40 mL) at room temperature. Then, the mixture was stirred at room temperature overnight. The mixture was filtered and the residue was washed with Et_2O to give of 62 (8.6 g, yield: 99.6%).

To a solution of 62 (8.6 g, 19.5 mmol) and DIEA (3.3 g, 25.2 mmol) in DCM (50 mL) was added 8-oxaspiro[4.5]decane-7,9-dione (4.2 g, 25.2 mmol) in DCM (10 mL) over 5 minutes under an ice bath. The progress of the reaction was checked by TLC. The solution was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE, 2% AcOH) to provide 63 (10 g, yield: 92.9%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.9-7.7 (d, 2H), 7.7-7.5 (m, 2H), 7.5-7.2 (m, 4H), 4.6-4.4 (m, 2H), 4.3-4.1 (m, 1H), 3.7-3.5 (m, 9H), 3.5-3.3 (m, 2H), 3.2-3.1 (m, 2H), 3.0-2.9 (m, 1H), 2.7-2.4 (m, 4H), 1.8-1.6 (m, 6H) 1.6-1.4 (m, 2H). LC-MS: m/z=575 $(M+23)^+$.

The resulting product 63 is used as intermediate 15 in Scheme 2 to produce compounds of the invention, such as Compounds 565, 568, 581, 582, and 585.

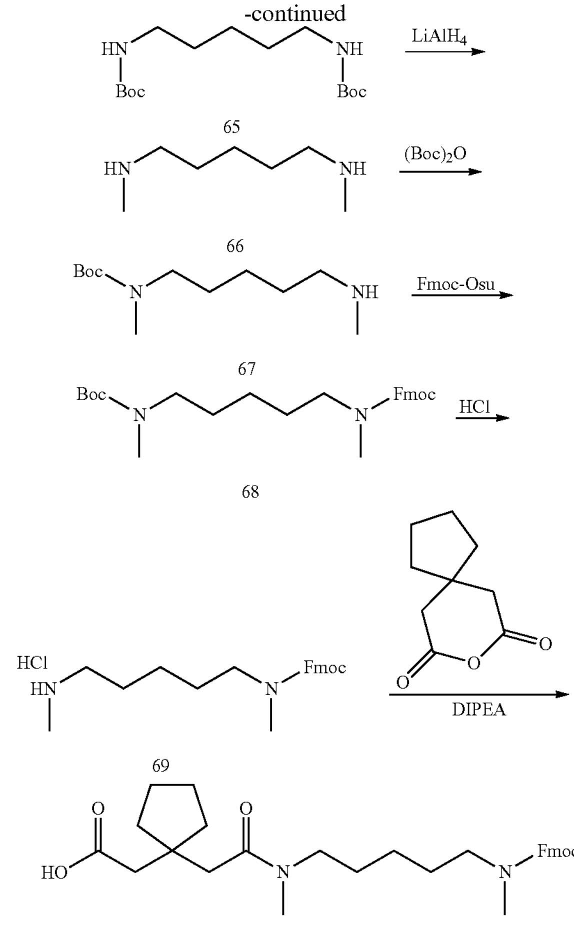
Example 11

Alternate Synthesis of 2-(1-(2-((5-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pentyl)(methyl)amino)-2-oxoethyl)cyclopentyl)acetic Acid (70)



64

-continued



To a solution of pentane-1,5-diamine (64; 10 g, 98 mmol) and potassium carbonate (27 g, 196 mmol) in 1,4-dioxane (50 mL) and H_2O (50 mL) was added $(Boc)_2O$ (42.8 g, 196 mmol) in 1,4-dioxane (50 mL) over 10 minutes under an ice bath. The reaction was stirred at room temperature for overnight. Then, the mixture solution was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The solvent was removed in vacuum to give 65 (26.1 g, yield 88.2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.7-4.5 (m, 2H), 3.2-3.0 (m, 6H), 1.8-1.7 (m, 2H), 1.6-1.4 (s, 18H), 1.4-1.3 (m, 2H).

To a solution of 65 (26.1 g, 86 mmol) in THF (200 mL) was added $LiAlH_4$ (13 g, 344 mmol) over 20 minutes under an ice bath. The reaction was refluxed for 16 h. After the reaction mixture was cooled, saturated NaOH (10 mL) was added. The mixture was filtered and the residue was washed with THF. Then, the filtrate was concentrated under vacuum to give 66 without purification (7 g, yield: 61.9%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.7-4.5 (m, 2H), 3.2-3.0 (m, 6H), 2.9-2.8 (m, 6H), 1.7-1.6 (m, 2H), 1.3-1.2 (m, 2H).

To a solution of 66 (7 g, 53.4 mmol) and potassium carbonate (14.7 g, 106.8 mmol) in 1,4-dioxane (30 mL) and H_2O (30 mL) was added $(Boc)_2O$ (11.6 g, 53.4 mmol) in 1,4-dioxane (30 mL) over 20 minutes under ice bath. The mixture was stirred at room temperature overnight. The reaction was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 50% EA/PE, 5% MeOH) to give 67 (6.2 g, yield: 50%).

To a solution of 67 (6.2 g, 26.9 mmol) and potassium carbonate (3.7 g, 26.9 mmol) in acetonitrile (25 mL) and water (25 mL) was added Fmoc-Osu (8.1 g, 24.3 mmol) in acetonitrile (25 mL) over 10 minutes under ice bath. The mixture was stirred for 30 minutes. After TLC, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE) to provide 68 (9.8 g, yield: 89.3%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.8-7.7 (d, 2H), 7.7-7.6 (m, 2H), 7.5-7.2 (m, 4H), 4.6-4.2 (m, 3H), 3.4-3.0 (m, 4H), 2.9-2.8 (m, 6H), 1.6-1.5 (s, 9H), 1.4-1.0 (m, 6H), 1-0.8 (m, 4H).

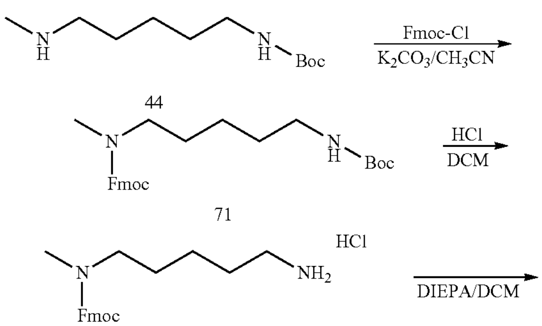
To a solution of 68 (9.8 g, 21.7 mmol) in 20 mL DCM was added Et_2O/HCl (5.2 mol/L, 20 mL) at room temperature. Then, the mixture was stirred at room temperature overnight. The mixture was filtered and the residue was washed with Et_2O to give 69 as a white solid (8.2 g, yield 97.6%). ^1H NMR (300 MHz, D_2O) δ: 7.9-7.7 (d, 2H), 7.7-7.5 (m, 2H), 7.5-7.3 (m, 4H), 4.6-4.4 (m, 2H), 4.3-4.2 (m, 1H), 3.4-3.2 (m, 1H), 3.2-3.0 (m, 1H), 2.9-2.8 (m, 3H), 1.7-1.6 (m, 2H), 1.6-1.2 (m, 3H), 1.0-0.8 (m, 3H).

To a solution of 69 (8.6 g, 22.1 mmol) and DIEA (8.5 g, 66.3 mmol) in DCM (50 mL) was added 8-oxaspiro[4.5]decane-7,9-dione (3.7 g, 22.1 mmol) in DCM (10 mL) over 5 minutes under an ice bath. The progress of the reaction was checked by TLC. Next, the solution was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE, 2% AcOH) to provide 70 (10 g, yield: 86.9%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.9-7.7 (d, 2H), 7.7-7.5 (m, 2H), 7.5-7.2 (m, 4H), 4.6-4.4 (m, 2H), 4.4-4.1 (m, 1H), 3.5-3.2 (m, 2H), 3.1-2.8 (m, 6H), 2.6-2.5 (m, 4H), 1.8-1.5 (m, 6H), 1.5-1.4 (m, 2H), 1.4-1.2 (m, 2H). LC-MS: m/z=520.4 $(M+23)^+$.

The resulting product 70 is used as intermediate 15 in Scheme 2 to produce compounds of the invention such as Compounds 600, 601, 623, 625, 626, 627, 628, 629, 630, 631, 644, 645, 646, 653, 665, 669, and 670.

Example 12

Synthesis of 2-(1-(2-(5-(((9H-fluoren-9-yl)methoxy)carbonyl)pentylamino)-2-oxoethyl)cyclopentyl)acetic Acid (73)

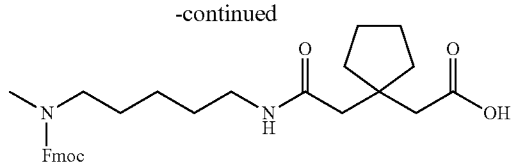


44

71

72

-continued



73

To a solution of 44 (from Example 8; 3.2 g, 14.8 mmol) and potassium carbonate (4.1 g, 29.6 mmol) in acetonitrile (20 mL) and water (40 mL) was added Fmoc-Cl (4.2 g, 16.3 mmol) in acetonitrile (20 mL) over 10 minutes under an ice bath. The mixture was stirred under an ice bath for about 2 h. The mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-30% EA/PE) to give 71 (4.3 g, yield: 66.2%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.9-7.8 (d, 2H), 7.7-7.6 (d, 2H), 7.5-7.4 (d, 2H), 7.4-7.3 (m, 2H), 4.5-4.4 (m, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 3.3-3.2 (m, 3H), 2.9-2.8 (m, 3H), 2.4 (m, 2H), 2.2 (m, 1H), 1.8-1.4 (s, 11H).

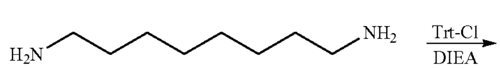
To a solution of 71 (4.3 g, 9.8 mmol) in 40 mL DCM was added Et_2O/HCl slowly (4 mol/L, 40 ml) under ice bath. Then, the mixture was stirred at RT overnight. The mixture was concentrated and washed with Et_2O to give 72 (3 g, yield 83.4%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.9-7.8 (d, 2H), 7.7-7.6 (d, 2H), 7.5-7.4 (d, 2H), 7.4-7.3 (m, 2H), 4.5 (m, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 3.3-3.2 (m, 3H), 2.9-2.8 (m, 3H), 2.4 (m, 2H), 2.2 (m, 1H), 1.8-1.4 (s, 2H).

To a solution of 72 (3 g, 8.0 mmol) and DIEA (2 g, 16.0 mmol) in DCM (20 mL) was added 8-oxaspiro[4.5]decane-7,9-dione (1.5 g, 8.8 mmol). The mixture was stirred at RT for 1 h. The mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-30% EA/PE, 2% AcOH) to give 73 (3.1 g, yield 77.5%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.9-7.8 (d, 2H), 7.7-7.6 (d, 2H), 7.6-7.5 (d, 2H), 7.4-7.3 (m, 2H), 7.3-7.2 (d, 2H), 4.5 (m, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 3.3-3.2 (m, 3H), 2.9-2.8 (m, 3H), 2.4 (m, 2H), 2.2 (m, 1H), 1.8-1.5 (s, 9H), 1.5-1.3 (s, 5H). LC-MS: m/z=529.2 $(M+23)^+$.

The resulting product 73 is used as intermediate 15 in Scheme 2 to produce compounds of the invention such as Compound 422. Alternatively, 73 was used as intermediate 11 in general Scheme 11 to produce compounds of the invention, such as Compounds 281, 307, 308, 335, 351, 363, 470 and 518.

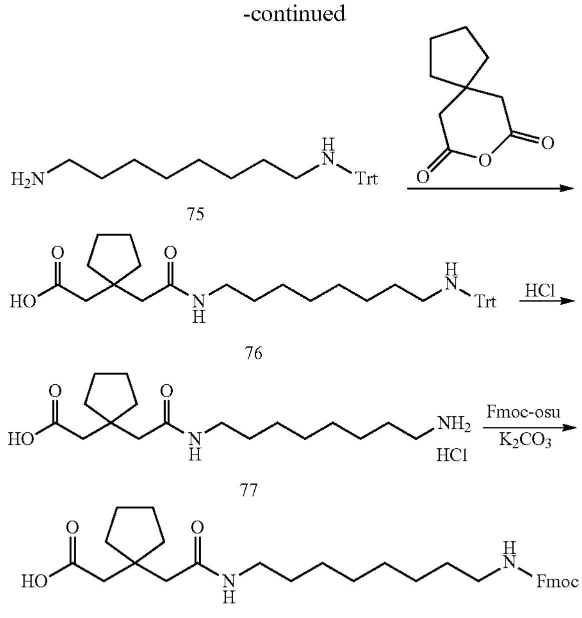
Example 13

Synthesis of 2-(1-(2-(8-(((9H-fluoren-9-yl)methoxy)carbonylamino)octylamino)-2-oxoethyl)cyclopentyl)acetic Acid (78)



74

-continued



75

76

77

78

To a solution of 74 (10 g, 69.5 mmol) and DIEA (8.9 g, 69.5 mmol) in DCM (100 mL) was added triphenylmethyl chloride (abbreviated as Trt-Cl) (9.66 g, 34.75 mmol) in DCM (20 mL) over 10 minutes under an ice bath. The mixture was stirred overnight at room temperature. After TLC, the mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 50% EA/PE-10% MeOH) to give 75 (8.8 g, yield 65.7%).

To a solution of 75 (8.8 g, 22.7 mmol) and DIEA (2.94 g, 22.7 mmol) in DCM (50 mL) was added 8-oxaspiro[4.5]decane-7,9-dione (3.82 g, 22.7 mmol) in DCM (10 mL) over 5 minutes under an ice bath. The progress of the reaction was checked by TLC. Next, the solution was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE, 2% AcOH) to give 76 (8.6 g, yield 68.3%).

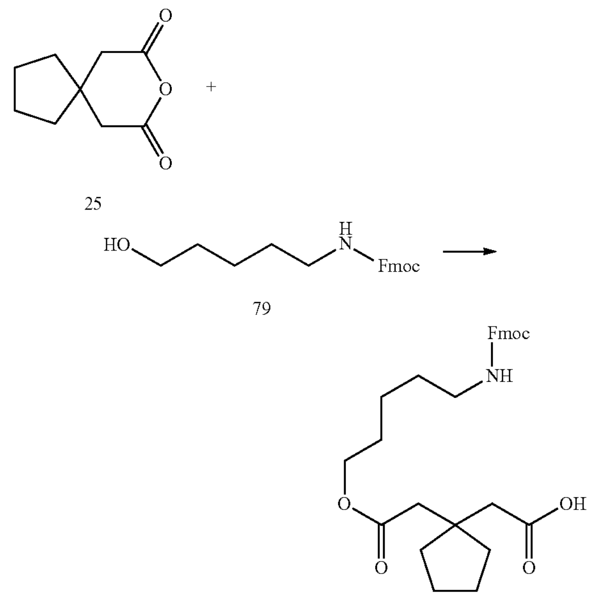
To a solution of 76 (8.6 g, 15.5 mmol) in 20 mL DCM was added Et_2O/HCl (5.2 mol/L, 10 mL) at room temperature. Then, the mixture was stirred at room temperature overnight. Next, the mixture was filtered and the residue was washed with Et_2O to give 77 as a white solid (4.6 g, yield 85%).

To a solution of 77 (4.6 g, 13.2 mmol) and potassium carbonate (3.6 g, 26.3 mmol) in acetonitrile (30 mL) and water (30 mL) was added Fmoc-Osu (4.44 g, 13.2 mmol) in acetonitrile (20 mL) over 10 minutes under ice bath. The mixture was stirred for 30 minutes. After TLC, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE) to give 78 (5.8 g, yield 82.3%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.8-7.7 (d, 2H), 7.7-7.6 (d, 2H), 7.5-7.3 (m, 4H), 4.5-4.4 (m, 2H), 4.4-4.3 (m, 2H), 3.3-3.1 (m, 4H), 2.5-2.4 (s, 2H), 2.4-2.3 (s, 2H), 1.8-1.7 (m, 4H), 1.7-1.6 (m, 2H), 1.6-1.4 (m, 6H), 1.4-1.3 (m, 9H). LC-MS: m/z=557.4 $(M+23)^+$.

The resulting product 78 is used as intermediate 15 in Scheme 2 to produce compounds of the invention, such as Compounds 337, 366, 441, 442, 505, 597, 598, and 599.

Example 14

Synthesis of 2-(1-(2-((5-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pentyl)oxy)-2-oxoethyl)cyclopentyl)acetic Acid



25

79

80

A 250-mL round bottom flask, equipped with magnetic stirring bar, is charged with 8-oxaspiro[4.5]decane-7,9-dione (25; 1.2 g, 7.1 mmoles), (9H-fluoren-9-yl)methyl(5-hydroxypentylcarbamate (79; 2.3 g, 7.1 mmoles), N,N-dimethylpyridin-4-amine (0.9 g, 7.4 mmoles), and dichloromethane (125 mL). The resulting mixture is stirred at room temperature for overnight. Next, the solvent was removed by rotary evaporation. The crude product is purified by silica gel chromatography (40 g, dichloromethane/acetonitrile: 100:0 to 50:50 ratio.) to obtain desired product 80 (1.67 g, 47.7%).

The resulting product 80 was then used as intermediate 11 in general Scheme 1 to produce compounds of the invention wherein —R^1-R^2— is —O—$(CH_2)_5$—NH—C(O)—C(H)(R^{11})—$(CH_2)_{0-2}$—, such as Compounds 671, 672, 673, 674, 675, 676, 677, 678, 679, 680 and 681.

Mass Spectrometry values for exemplary compounds of the invention are set forth in Table 2. NMR data for select compounds are set forth after Table 2.

TABLE 2

Physical data for Exemplary Compounds of the Invention.

Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
100	756.38	756.33
101	841.43	841.34
102	742.36	742.21
103	827.42	827.3

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.		
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
104	823.44	823.38
105	841.42	841.34
106	841.42	841.34
107	841.42	841.34
108	813.39	813.32
109	827.41	827.37
110	855.44	855.39
111	869.46	869.36
112	857.39	857.31
113	843.37	843.26
114	823.44	823.3
115	809.43	809.33
116	841.43	841.34
117	827.42	827.3
118	841.25	841.34
119	827.42	827.3
120	901.35	901.29
121	887.34	887.25
122	789.46	789.37
123	775.44	775.33
124	899.47	899.44
125	885.46	885.4
126	837.46	837.35
127	823.44	823.38
128	827.42	827.37
129	756.38	756.33
130	742.36	742.28
131	742.36	742.28
132	875.42	875.34
133	861.40	861.37
134	861.40	861.37
135	875.42	875.34
136	827.42	827.3
137	827.42	827.37
138	823.44	823.38
139	809.43	809.33
140	891.43	891.31
141	829.37	829.22
142	815.36	815.25
143	829.37	829.22
144	815.36	815.25
145	857.40	857.31
146	843.39	843.26
147	859.38	859.23
148	845.37	845.26
149	813.40	813.25
150	799.39	799.28
151	799.39	799.28
152	667.30	667.18
153	695.33	695.20
154	709.35	709.17
155	723.37	723.21
156	743.33	743.17
157	757.35	757.22
158	771.37	771.19
159	771.37	771.34
160	785.38	785.23
161	799.40	799.20
162	757.35	757.14
163	681.32	681.15
164	771.37	771.19
165	695.33	695.2
166	785.38	785.23
167	709.35	709.17
168	815.39	815.25
169	739.36	739.18
170	829.41	829.22
171	753.38	753.22
172	843.42	843.26
173	767.39	767.27
174	827.42	827.22
175	827.42	827.22
176	827.42	827.22
177	799.39	799.20

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.		
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
178	871.44	871.28
179	742.36	742.21
180	815.36	815.17
181	815.36	815.25
182	843.39	843.26
183	753.40	753.22
184	773.39	773.18
185	805.33	805.35
186	729.44	729.97
187	815.32	815.71
188	785.38	785.75
189	769.39	769.77
190	789.38	789.96
191	821.32	821.92
192	745.43	745.95
193	801.38	801.95
194	758.34	758.83
195	758.34	758.83
196	748.31	748.84
197	771.34	771.84
198	775.33	775.91
199	772.35	772.95
200	759.33	759.86
201	759.33	759.86
202	772.35	772.95
203	775.33	775.91
204	791.30	791.89
205	791.30	791.89
206	737.37	737.35
207	763.39	763.37
208	758.34	758.9
209	773.35	773.92
210	807.31	807.72
211	831.31	831.91
212	772.35	772.95
213	772.35	772.95
214	773.34	773.84
215	773.34	773.84
216	787.35	787.89
217	787.35	787.89
218	801.37	801.95
219	787.35	787.31
220	765.37	765.92
221	717.32	717.38
222	745.35	745.4
223	785.38	785.39
224	806.31	806.31
225	822.26	822.27
226	772.35	772.3
227	775.33	775.4
228	743.36	743.40
229	743.36	743.40
230	727.38	727.43
231	703.42	703.48
232	744.36	744.36
233	793.38	793.37
234	725.34	725.36
235	748.31	748.35
236	777.40	777.33
237	737.40	737.34
238	751.42	751.38
239	771.37	771.34
240	771.37	771.34
241	805.33	805.27
242	772.35	772.30
243	711.37	711.32
244	701.40	701.19
245	675.39	675.39
246	715.42	715.38
247	689.40	689.36
248	753.34	753.16
249	845.37	845.34
250	816.35	816.29
251	703.42	703.41

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.

Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
252	627.39	627.42
253	719.42	719.45
254	690.40	690.4
255	717.35	717.38
256	641.31	641.39
257	733.34	733.35
258	704.33	704.37
259	756.39	756.34
260	802.37	802.32
261	861.41	861.38
262	877.41	877.34
263	772.39	772.38
264	739.32	739.26
265	831.35	831.29
266	802.34	802.24
267	834.47	834.39
268	825.47	825.37
269	901.46	901.29
270	731.30	731.28
271	793.32	793.30
272	807.33	807.30
273	710.34	710.28
274	724.36	724.26
275	779.39	779.33
276	793.42	793.30
277	791.33	791.22
278	791.33	791.29
279	787.36	787.16
280	785.38	785.31
281	785.38	785.31
282	787.44	787.38
283	754.37	754.38
284	856.38	856.28
285	829.37	829.30
286	785.38	785.31
288	785.38	785.31
289	799.40	799.29
290	785.38	785.31
291	799.40	799.36
292	760.35	760.30
293	743.45	743.40
294	759.45	759.22
295	747.43	747.24
296	807.34	807.27
297	793.33	793.30
298	807.34	807.27
299	801.34	801.28
300	778.41	778.29
301	764.39	764.32
302	786.37	786.48
303	738.37	738.30
304	780.39	780.29
305	789.36	789.23
306	789.36	789.23
307	801.38	801.28
308	789.36	789.31
309	865.39	865.30
310	703.42	703.33
311	703.42	703.33
312	703.42	703.33
313	689.40	689.36
314	689.40	689.36
315	729.44	729.36
316	773.42	773.34
317	861.41	861.50
318	772.35	772.40
319	801.38	801.40
320	857.44	857.60
321	815.39	815.40
322	829.37	829.50
323	786.37	786.40
324	795.31	795.30
325	825.34	825.23
326	811.32	811.26

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.

Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
327	759.34	759.29
328	811.32	811.26
329	811.32	811.26
330	773.34	773.27
331	819.48	819.53
332	743.45	743.44
333	718.42	718.45
334	714.46	714.45
335	743.45	743.40
336	849.49	849.60
337	744.47	744.40
338	772.36	772.43
339	815.35	815.39
340	801.37	801.38
341	842.40	842.45
342	743.45	743.59
343	773.46	773.61
344	748.43	748.54
345	728.36	728.28
346	686.43	686.50
347	742.37	742.41
348	700.44	700.55
349	770.37	770.50
350	728.48	728.58
351	773.46	773.54
352	774.42	774.50
353	772.36	772.43
354	758.37	758.45
355	716.44	716.51
356	772.38	772.50
357	730.46	730.57
358	800.42	800.53
359	758.49	758.60
360	773.46	773.54
361	730.43	730.47
362	716.42	716.45
363	841.44	841.55
364	770.37	770.43
365	784.38	784.48
366	742.37	742.48
367	829.37	829.42
368	816.35	816.41
369	787.44	787.47
370	774.42	774.43
371	806.46	806.51
372	812.45	812.50
373	765.42	765.55
374	765.42	765.55
375	759.44	759.56
376	731.41	731.39
377	653.40	653.38
378	745.43	745.36
379	715.42	715.37
380	747.62	747.41
381	730.43	730.43
382	733.41	733.38
383	805.47	805.48
384	760.41	760.45
385	865.34	865.45
386	789.36	789.44
387	799.40	799.49
388	807.35	807.47
390	785.38	785.51
391	700.33	700.48
392	714.34	714.53
393	730.34	730.50
394	744.35	744.48
395	735.45	735.48
396	749.38	749.51
397	716.32	716.38
398	686.31	686.36
399	729.35	729.42
400	746.33	746.40
401	716.32	716.53

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.

Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
402	759.36	759.49
403	733.41	733.53
404	783.41	783.52
405	933.44	933.62
406	747.33	747.30
407	715.46	715.50
408	819.37	819.38
409	645.38	645.39
410	676.39	676.58
411	715.34	715.27
412	745.35	745.29
413	785.38	785.44
414	815.39	815.46
415	723.39	723.55
416	890.44	890.59
417	705.40	705.40
418	740.36	740.39
420	687.31	687.28
421	673.41	673.41
422	673.41	673.41
423	660.34	660.40
424	736.41	736.40
425	871.43	871.50
425	871.43	871.83
426	891.42	891.47
427	829.39	829.51
428	822.37	822.49
429	822.37	822.49
430	982.58	982.71
431	948.48	948.62
432	842.44	842.52
433	876.42	876.54
434	821.36	821.52
435	880.40	880.42
436	807.46	807.44
437	906.55	906.63
438	1024.51	1024.56
439	990.49	990.55
440	827.28	827.37
441	772.39	772.43
442	743.37	743.39
443	786.37	786.48
444	863.39	863.52
445	877.41	877.50
446	770.35	770.43
447	772.36	772.44
448	699.42	699.46
449	766.43	766.51
450	766.43	766.51
451	832.35	832.39
452	771.37	771.39
453	776.34	776.40
454	815.36	815.46
455	875.38	875.49
456	682.30	682.29
457	801.38	801.41
458	697.41	697.52
459	844.38	844.52
460	776.32	776.60
461	774.33	774.60
462	857.44	857.92
463	775.36	775.66
464	699.33	699.59
465	700.31	700.40
466	731.33	731.62
467	745.35	745.61
468	709.35	709.73
469	817.39	817.80
470	817.39	817.80
471	871.43	871.98
472	887.39	887.96
473	873.40	873.90
474	803.37	803.84
475	796.33	796.81

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.

Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
476	783.43	783.86
477	792.36	792.82
478	758.40	758.86
479	860.39	860.90
480	831.40	831.90
481	728.37	728.70
482	845.38	845.44
483	801.38	801.44
484	776.34	776.41
485	744.37	744.44
486	817.39	817.48
487	815.39	815.50
488	831.40	831.47
489	845.42	845.42
490	778.34	778.45
491	810.38	810.47
492	803.37	803.45
493	851.37	851.43
494	774.37	774.46
495	774.37	774.46
496	774.37	774.46
497	756.33	756.40
498	796.37	796.50
499	885.45	885.50
500	759.33	759.40
501	799.37	799.50
502	796.33	796.40
503	743.37	743.50
504	818.37	818.53
505	814.41	814.54
506	899.46	899.64
507	877.43	877.54
508	838.38	838.57
509	837.47	837.61
510	798.42	798.57
511	823.46	823.63
512	815.43	815.57
513	873.38	873.47
514	929.44	929.51
515	840.45	840.56
516	731.38	731.60
518	831.40	831.54
519	771.36	771.58
520	849.37	849.59
521	764.32	764.46
522	746.33	746.44
523	769.39	769.54
523	769.39	769.58
523	769.39	769.51
524	908.43	908.70
525	817.39	817.60
526	771.36	771.60
527	930.40	930.55
528	904.38	904.54
529	847.36	847.51
530	814.32	814.46
531	820.38	820.51
532	802.39	802.51
533	848.37	848.54
534	830.38	830.43
535	789.35	789.47
536	807.34	807.45
537	762.33	762.41
538	780.32	780.45
539	846.41	846.63
540	864.40	864.67
541	830.38	830.45
542	848.37	848.51
543	803.37	803.60
544	776.34	776.53
545	776.34	776.53
546	730.34	730.54
547	730.34	730.54
548	774.33	774.53

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.

Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
549	799.36	799.60
550	801.37	801.60
551	801.37	801.60
552	828.42	828.66
553	803.39	803.60
554	775.34	775.50
555	784.36	784.56
556	916.40	916.67
557	840.37	840.64
558	764.33	764.55
559	814.32	814.46
560	839.35	839.53
561	803.37	803.60
562	871.46	871.63
563	872.43	872.58
564	775.34	775.57
565	810.34	810.54
566	849.39	849.66
567	851.37	851.60
568	714.33	714.53
569	755.35	755.54
570	753.37	753.59
571	762.33	762.43
572	780.32	780.45
573	842.40	842.56
574	830.40	830.58
575	805.35	805.59
576	801.37	801.60
577	739.36	739.56
578	753.37	753.53
579	714.33	714.49
580	728.34	728.54
581	790.36	790.43
582	817.41	817.49
583	831.38	831.47
584	858.43	858.53
585	788.34	788.43
586	787.36	787.40
587	844.42	844.54
588	768.39	768.47
589	788.38	788.44
590	806.37	806.47
591	824.36	824.45
592	789.35	789.47
593	818.34	818.38
594	829.37	829.62
595	754.40	754.49
596	761.46	761.52
597	792.37	792.50
598	750.44	750.50
599	757.50	757.60
600	807.46	807.59
601	814.52	814.68
602	809.44	809.58
603	816.50	816.61
604	822.47	822.60
605	829.53	829.68
606	787.38	787.50
607	755.37	755.47
608	773.36	773.50
609	741.35	741.48
610	759.34	759.45
611	768.41	768.47
612	636.38	636.41
613	782.43	782.45
614	789.49	789.54
615	754.40	754.42
616	761.46	761.52
617	789.35	789.47
618	803.37	803.45
619	817.39	817.49
620	777.35	777.42
621	817.39	817.49
622	819.36	819.42

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.

Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
623	789.47	789.54
624	672.40	672.49
625	711.44	711.38
626	871.54	871.48
627	926.45	926.42
628	814.41	814.36
629	891.43	891.38
630	821.39	821.39
631	841.45	841.45
632	658.38	658.33
633	872.34	872.36
634	872.34	872.36
635	836.34	836.33
636	850.35	850.32
637	928.40	928.37
638	928.40	928.37
639	881.38	881.39
640	775.48	775.45
641	936.46	936.51
642	908.43	908.47
643	790.40	790.41
644	848.51	848.47
645	906.41	906.54
646	844.50	844.55
647	734.41	734.39
649	943.36	943.39
650	886.47	886.42
651	904.38	904.33
652	722.29	722.20
653	858.51	858.46
654	814.37	814.36
655	839.45	839.44
656	902.39	902.40
657	936.41	936.51
658	942.36	942.43
659	978.42	978.45
660	901.43	901.44
661	974.42	974.38
662	925.40	925.41
663	772.44	772.40
664	742.43	742.38
665	770.46	770.42
666	822.36	822.29
667	950.40	950.34
668	908.47	908.41
669	892.40	892.34
670	850.47	850.42
671	766.39	766.42
672	690.36	690.37
673	654.38	654.41
674	808.32	808.30
675	732.29	732.31
676	696.31	696.14
677	718.39	718.27
678	822.34	822.20
679	780.41	780.33
680	732.41	732.24
681	668.39	688.39

NMR Data.

Compound 159:

^{1}H NMR (300 MHz, DMSO-d6) δ 9.96 (1H, s), 8.51 (3H, m), 8.01 (1H, t), 7.44 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.24-7.12 (8H, m), 6.95 (1H, t), 4.76 (1H, q), 4.20 (1H, m), 3.76 (1H, dd), 3.50 (1H, dd), 3.44 (2H, d), 3.17-2.87 (7H, m), 2.76 (1H, m), 2.21 (2H, q), 2.12 (1H, d), 1.76 (1H, d), 1.65 (1H, m), 1.60-1.47 (3H, m), 1.45-1.29 (7H, m), 1.19 (3H, m), 0.86 (1H, m).

Compound 181:

^{1}H NMR (300 MHz, DMSO-d6) δ 12.46 (1H, br), 9.98 (1H, s), 8.51 (3H, m), 8.23 (1H, d), 7.46 (2H, d), 7.37 (1H, dd), 7.28 (1H, dd), 7.26-7.12 (9H), 7.06 (1H, t), 4.76 (1H, q), 4.19 (2H, m), 3.75 (1H, dd), 3.49 (1H, dd), 3.44 (2H, d), 3.18-2.93 (5H), 2.76 (1H, m), 2.21 (2H, d), 2.14 (1H, d), 1.85 (1H, d), 1.70-1.58 (3H), 1.58-1.47 (3H), 1.47-1.16 (7H), 0.91 (1H, m).

Compound 239:

^{1}H NMR (300 MHz, DMSO-d6) δ 10.07 (1H, s), 8.54 (3H, m), 8.01 (1H, t), 7.45 (2H, d), 7.36 (1H, s), 7.26-7.15 (8H, m), 7.09 (2H, d), 6.95 (1H, t), 4.65 (1H, m), 4.20 (1H, m), 3.76 (1H, dd), 3.52-3.35 (4H, m), 3.30-2.70 (8H, m), 2.21 (2H, dd), 2.12 (1H, d), 1.77 (1H, d), 1.65 (1H, m), 1.60-1.30 (11H, m), 1.18 (2H, m), 0.86 (1H, m).

Compound 242:

^{1}H NMR (300 MHz, DMSO-d6) δ 9.96 (1H, s), 8.48 (2H, m), 8.29 (1H, d), 7.43 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.24-7.10 (9H, m), 4.75 (1H, m), 4.27 (1H, m), 4.11 (1H, m), 3.79 (2H, m), 3.43 (2H, q), 3.35 (1H, d), 3.20-2.60 (8H, m), 2.28 (1H, d), 2.16 (1H, d), 2.12 (1H, s), 1.65-1.36 (12H, m), 1.25 (1H, m), 1.06 (1H, m).

Compound 244:

^{1}H NMR (300 MHz, DMSO-d6) δ 9.97 (1H, s), 8.53 (2H, m), 8.34 (1H, d), 8.01 (1H, t), 7.87 (2H, d), 7.27 (3H, m), 7.20 (2H, d), 6.95 (1H, t), 4.46 (1H, q), 4.20 (1H, m), 3.76 (1H, dd), 3.49 (3H, m), 3.09 (2H, m), 2.95 (1H, dd), 2.88 (1H, m), 2.76 (1H, m), 2.21 (2H, q), 2.12 (1H, d), 1.76 (1H, d), 1.63 (2H, m), 1.57-1.30 (11H, m), 1.18 (2H, m), 0.86 (1H, m), 0.70 (1H, m), 0.32 (2H, m), 0.06 (2H, m).

Compound 256:

^{1}H NMR (300 MHz, DMSO-d6) δ 12.50 (1H, br), 9.97 (1H, s), 9.23 (1H, br), 8.54 (2H, m), 8.37 (1H, d), 8.10 (1H, m), 7.44 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.24-7.14 (4H, m), 7.06 (1H, t), 6.92 (2H, d), 6.60 (2H, d), 4.73 (1H, q), 4.22 (1H, m), 4.13 (1H, q), 3.75 (1H, dd), 3.48 (1H, dd), 3.17-2.93 (6H, m), 2.77 (1H, dd), 2.24 (2H, d), 2.12 (1H, d), 1.87 (1H, d), 1.69-1.16 (15H, m), 0.93 (1H, m).

Compound 181:

^{1}H NMR (300 MHz, DMSO-d6) δ 12.46 (1H, br), 9.98 (1H, s), 8.51 (3H, m), 8.23 (1H, d), 7.44 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.25-7.11 (8H, m), 7.06 (1H, t), 4.76 (1H, q), 4.19 (2H, m), 3.75 (1H, dd), 3.49 (1H, dd), 3.44 (1H, d), 3.18-2.93 (5H, m), 2.76 (1H, m), 2.24 (2H, d), 2.14 (1H, d), 1.85 (1H, d), 1.70-1.6 (3H, m), 1.58-1.47 (3H, m), 1.46-1.16 (7H, m), 0.91 (1H, m).

Compound 453:

^{1}H NMR (300 MHz, DMSO-d6) δ 9.93 (1H, s), 9.24 (1H, s), 8.41 (2H, q), 8.23 (1H, q), 7.59 (1H, t), 7.41 (2H, d), 7.36 (1H, dd), 7.26 (1H, dd), 7.20 (1H, td), 7.15 (2H, m), 7.00 (1H, t), 6.61 (1H, m), 6.56 (2H, m), 4.74 (1H, q), 4.37 (1H, m), 3.53-3.33 (12H, m), 3.16-2.94 (5H, m), 2.71 (1H, q), 2.37 (1H, d), 2.23 (1H, d), 2.01 (1H, d), 1.69 (1H, d), 1.64-1.36 (5H, m), 1.09 (1H, m), 1.00 (1H, m), 0.77 (1H, m).

Compound 474:

^{1}H NMR (300 MHz, DMSO-d6) δ 9.98 (1H, s), 8.49 (1H, d), 8.20 (1H, d), 7.99 (2H, m), 7.44 (2H, d), 7.37 (1H, d), 7.25 (2H, td), 7.18 (5H, m), 7.05 (2H, t), 7.56 (1H, m), 4.76 (1H, m), 4.21 (2H, m), 3.42 (4H, m), 3.27-2.83 (8H, m), 2.27 (2H, t), 2.05 (1H, d), 1.75 (2H, m), 1.52 (3H, m), 1.44-1.28 (6H, m), 1.22 (2H, d), 1.16 (2H, m), 0.83 (1H, m).

Compound 566:

^{1}H NMR (300 MHz, DMSO-d6) δ 9.97 (1H, s), 8.54 (2H, m), 8.37 (1H, d), 8.10 (1H, br), 7.44 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.22 (1H, dd), 7.18 (3H, m), 7.06 (1H, t), 6.92 (2H, d), 6.61 (2H, d), 4.74 (1H, q), 4.22 (1H, m), 4.13 (1H, q), 3.76 (1H, dd), 3.48 (1H, dd), 3.29 (5H, m), 3.18-2.94 (6H, m), 2.77 (1H, q), 2.24 (2H, d), 2.13 (1H, d), 1.87 (1H, d), 1.68-1.19 (15H, m), 0.93 (1H, m).

Compound 406:

^{1}H NMR (300 MHz, DMSO-d6) δ 10.01 (1H, s), 9.05 (1H, d), 8.99 (1H, dd), 8.72 (1H, dd), 8.43 (1H, d), 8.22 (2H, m), 7.59 (1H, t), 7.55 (1H, q), 7.46 (2H, d), 7.40 (2H, m), 7.22 (2H, m), 7.17 (2H, d), 4.97 (1H, m), 4.37 (1H, m), 3.51-3.28 (11H, m), 3.19 (1H, q), 3.09 (1H, m), 2.97 (2H, m), 2.71 (1H, q), 2.36 (1H, d), 2.23 (1H, d), 2.00 (1H, d), 1.68 (1H, d), 1.61 (1H, m), 1.55-1.33 (4H, m), 1.08 (1H, m), 1.00 (1H, m), 0.77 (1H, m).

Compound 528:

^{1}H NMR (300 MHz, DMSO-d6) δ 12.41 (1H, br), 9.99 (1H, s), 8.50 (1H, d), 8.38 (1H, d), 8.25 (1H, d), 8.00 (1H, d), 7.46 (1H, d), 7.41-7.11 (9H), 7.06 (2H, t), 6.77 (1H, s), 4.78 (1H, m), 4.17 (3H, m), 3.24-3.08 (3H), 3.08-2.90 (3H), 2.72 (1H, m), 2.29 (2H, dd), 2.10 (3H, m), 1.95 (1H, m), 1.88-1.22 (15H), 1.79 (1H, m), 1.05 (1H, m), 0.74 (1H, m).

Compound 556:

^{1}H NMR (300 MHz, DMSO-d6) δ 10.28 (1H, s), 8.56 (1H), 8.43 (1H), 8.01 (1H), 7.82 (1H), 7.47 (2H, d), 7.38 (1H, d), 7.30 (2H), 7.26-7.14 (4H), 7.10 (2H), 6.88-6.7 (2H), 5.12 (1H), 4.77 (1H), 4.44 (2H), 4.30-4.10 (2H), 4.00 (1H), 3.43 (2H), 3.24-3.00 (4H), 2.90 (1H), 2.71 (1H), 2.43 (2H), 2.27 (2H), 2.07 (2H), 1.95 (2H), 1.86-1.00 (15H), 0.76 (1H).

Example 15

Evaluation of Biological Activity

Exemplary compounds were tested for the ability to bind to and modulate IL-17 activity in one or more of the below-described assays. Experimental procedures and results are provided below.

Experimental Procedures:

A. IL-17 ELISA Assay.

ELISA I: The ability of the compounds to block binding of IL17a to its receptor, IL17R, was analyzed in a competition ELISA format. High binding 96-well plates (Costar #9018) were coated with 20 nM of recombinant human IL17a (R&D Systems #317-ILB) in PBS (0.64 μg/mL), 100 μL/well, for 30 min at 37'C followed by 5 min at 4'C. Plates were then washed in PBST (PBS/0.05% Tween-20) on a plate washer, (Biotech EL-450) blocked with protein-free blocking buffer (Thermo Scientific #37573) in 250 μL/well for 30 min on shaker at room temperature, and then washed again. Compound dilutions prepared in PBST were added into the wells in duplicates followed by the addition of IL17R/Fc (R&D Systems #177-IR) at a final concentration of 12 nM. Plates were then incubated for 30 min at room temperature on the shaker. Wells with no compound served as a positive "no competitor" control, while wells with no IL17R/Fc and no compound served as a blank negative control. After an additional PBST wash, 50 ng/mL HRP-conjugated goat anti-human Fc IgG (KPL #04-10-20) was added to the plate for 30 min at room temperature, followed by PBST wash and addition of SureBlue™ TMB (KPL #52-00-03). After the sufficient color development, the reaction was fixed by the addition of 100 μL/well 0.5 N HCl and absorbance was measured at 450 nm on Biotek plate reader. The absorbances of 'no competitor' control and blank control did not exceed 1.0 A.U. and 0.05 A.U. respectively.

Data were processed using BioAssay Enterprise v10.1.4 (CambridgeSoft) software. Linear OD λ450 were plotted against log concentration (x) and fitted to a 4-parameter logistic equation. IC_{50} was calculated using positive 'no competitor' control data as an upper limit and blank control as a lower limit in each assay.

ELISA II:

In this version, a high binding 96-well plate (Costar #9018) was coated with 20 nM of goat anti-human IgG (KPL 01-10-02) in PBS, 100 μL/well, for 30 min at 37° C. followed by 5 min at 4° C. The plate was then washed in PBST (PBS/0.05% Tween-20) on a plate washer, (BioTek ELx450) then blocked with protein-free blocking buffer (Thermo Scientific #37573) in 250 μL/well for 30 min on a shaker at room temperature, and then washed again. IL17R/Fc (R&D Systems #177-IR; 10 nM in PBST, 100 μL/well) was then added to all wells. The plate was then incubated for 30 minutes at room temperature on the shaker.

While the receptor capture step was underway, compound dilutions were prepared in PBST to a concentration of 1 μM in 1.5 mL tubes. After the receptor capture step, the plate was washed and 50 μL PBST was added to the wells in row B down to row H. Then, 62.5 μL of the 1 μM compound dilutions were added to the wells of row A. From row A, 12.5 μL of the compound solution was removed and added to row B with mixing and this process of 5-fold dilutions was continued, by row, to row G. One of the wells in row A received only PBST (62.5 μL) and this dilution series served as the no competitor control. Then, going up from row G to row A, 50 μL of b-IL-17 (biotinylated human IL-17, R&D Systems #317-ILB; 20 nM) was added to all wells. Row H received 50 μL of PBST and served as the blank row, i.e., no compound and no b-IL-17. The plate was then incubated for 30 minutes at room temperature on the shaker.

After the wash, 100 μL Streptavidin-Horseradish Peroxidase (SA-HRP) (KPL #14-30-00) at 25 ng/mL in PBST was added to each well in the plate and the plate incubated for 30 minutes at room temperature followed by wash and 100 μL SureBlue™ TMB (KPL #52-00-03). After sufficient color development (approx 3-6 minutes), the reaction was fixed by the addition of 100 μL/well 0.5 N HCl and absorbance was measured at 450 nm on a BioTek Synergy 2 plate reader. The absorbances of 'no competitor' control and blank control should not exceed 1.5 A.U. and 0.06 A.U., respectively.

Data was processed using BioAssay Enterprise v10.1.4 (CambridgeSoft) software. Linear OD λ450 were plotted against log concentration (x) and fitted to a 4-parameter logistic equation. IC50 was calculated using positive 'no competitor' control data as an upper limit and blank control as a lower limit in each assay.

B. Surface Plasmon Resonance (SPR) Analysis of Compound Interactions with IL17A

SPR analysis was carried out with a GE Healthcare (Piscataway, N.J.) Biacore X100 system. Typically, the chip (NTA Biacore Biosensor chip; GE Healthcare BR-1000-34) was first conditioned by injection of 0.35 M EDTA, which also served to remove any immobilized proteins from previous runs. Before immobilization of the recombinant 6-His-tagged IL17, the chip was washed with 0.5 mM nickel chloride in NTA buffer (10 mM HEPES buffer, 0.15 M sodium chloride, 10 μM ethylene diamine tetraacetic acid, 0.005% v/v surfactant P20 (GE Healthcare BR-1000-54)) to form a nickel chelate on the chip. IL17 protein was immobilized onto a NTA chip through its 6-His tag. IL17A was typically injected at 0.25 μM for 60-120 seconds, followed by a stabilization step washing with NTA+0.5% DMSO for 120 seconds or longer.

Five 2-fold or 3-fold serial dilutions of test compound were injected serially onto the chip. All steps were conducted using NTA buffer containing 0.5% v/v dimethylsulfoxide (DMSO). Compounds were diluted from stock solutions of 10 mM concentration in 100% DMSO with NTA buffer to obtain 50 μM solutions in NTA+0.5% DMSO. Subsequent 2× or 3× dilutions were made in NTA+0.5% DMSO. Compound was generally injected for 180 seconds followed by washing the chip in buffer alone for 120 seconds. The rate of refractive index change (RU units/time) and the maximum extend of RU change was measured during the "on" phase of analyte injection, followed by measuring the rate during the "off" phase.

Kinetic parameter fits were conducted using the Biacore SPR Evaluation Program (GE Healthcare) for 1:1 molecular binding fits, after subtracting the baseline average of 2 or more runs in which no analyte was injected. This program then reports the best fit average for the "on" rate (Ka), the "off" rate (Kd) and the dissociation constant (KD) (Chaiken, I et al., Anal Biochem 201, 197-210 (1992)). A separate program in the Biacore SPR Evaluation Program then calculates the best fit for Kd based upon the extent of binding alone (RU units bound) at each concentration of analyte and reports the best fit Kd by best fit to a Lineweaver-Burke plot. Typically, the Kd value calculated through both means agreed within a factor of three.

The presence and activity of IL17 on the NTA chip was routinely confirmed three ways:

1) An increase in response units (RU) upon immobilization confirms that the IL17 was immobilized on the chip;
2) Anti-IL17 was also injected on the chip to confirm the presence of IL17; and
3) IL17R was injected onto the chip to confirm that the immobilized IL17 retained its binding activity for its receptor.

Negative controls to access specificity for compound binding were conducted by immobilizing unrelated, but his-tagged, proteins (such as cyclophilin D) and conducting the same analysis as done with IL17A.

C. Inhibition of IL17A Induced Secretion of IL6 in Human Rheumatoid Arthritis Synovial Fibroblast Cells

This assay was used to determine the extent of inhibition of IL-17A induced secretion of IL-6 in primary human rheumatoid synovial fibroblast (RASF) cells by compounds of the invention. IL-17A is known to stimulate IL-6 production in RASF cells.

Low passage (passage 2-8) Primary human RASF cells (Asterand) were maintained in maintenance medium. Cells were detached from flasks by tryptic digestion and the cell density of the suspension determined. To each well of a 96 well culture plate was added 100 μL of seeding medium containing 50,000 cells/mL and the plate incubated overnight in a humidified 37° C., 5% CO_2 incubator. The medium was replaced with fresh assay medium and cells were incubated for additional 5 hours in a humidified 37° C., 5% CO_2 incubator prior to stimulation with recombinant human IL-17A ("rhIL-17A"). Prior to addition to cells, rhIL-17A (30 ng/mL) in assay medium was incubated with either DMSO alone, compounds, or anti-IL17 receptor antibody (3 μg/mL) for 1 hour at 37° C. The final concentration of DMSO in all samples was 0.25%. The final concentration of compounds varied from 0.03 μM to 25 μM.

Immediately before stimulation, cells were washed once with fresh assay medium. Then, 100 μL of the test samples was added in triplicate wells and the plates incubated for 20 hours in a humidified 37° C., 5% CO_2 incubator. The assay medium from each well was collected and the IL-6 concentration in cell culture supernatants was determined by ELISA either immediately or after storage at −20° C.

A water-soluble tetrazolium salt (WST1) viability assay was immediately performed on the cells after the conditioned medium was collected using a WST1 reagent purchased from Roche. The concentration of IL-6 obtained from ELISA was normalized by the WST1 data.

D. HT-29 Cellular Assay

To test the ability of a compound of the invention to neutralize or antagonize IL-17 bioactivity, the following cell-based assay was used. IL-17 can stimulate epithelial cells and other cells to secrete GROα. The ability of a compound of the invention to neutralize IL-17-induced GROα secretion from the human colorectal adenocarcinoma epithelial cell line HT-29 is tested in this assay.

HT-29 cells (human colorectal adenocarcinoma epithelial cells, ATCC #HTB-38), were maintained in culture/assay medium in tissue culture-treated flasks using standard techniques. HT-29 cells were grown in tissue culture flasks until they were 50-80% confluent on the day before the assay. The day before the assay, the cells were detached from the culture flasks with trypsin+EDTA. The trypsin was inactivated with complete assay medium. HT-29 cells were then centrifuged at 500×g for 5 minutes at room temperature. The cell pellet was then re-suspended in Defined Keratinocyte SFM (Invitrogen #10766019)+10% FCS and 50,000 HT-29 cells (in 100 μl) were added to each treatment well of the 96-well plates. The 96-well plates were placed in a tissue culture incubator (37° C., 5% CO_2) overnight. The next day, the media was removed from the cells and the cells were washed twice with Defined Keratinocyte SFM. In a separate 96-well plate, compounds to be tested were serially diluted in Defined Keratinocyte SFM and run in triplicate in 100 μL total volume. To these compound samples were then added 100 μL of human IL-17 at a concentration of 20 ng/mL in Defined Keratinocyte SFM for serum-free assays. 150 μL of the compound/IL-17 mixture was then added to the cells from which the media has previously been removed. The cells were grown for 48 hours in Defined Keratinocyte SFM in a tissue culture incubator (37° C., 5% CO_2).

At the end of the incubation, the plates are centrifuged (500×g for 5 minutes at room temperature), and the cell culture media is transferred to polypropylene 96-well plates. The supernatant was used neat in the ELISA. GROα levels are measured with a GROα sandwich ELISA (R+D Systems DuoSet #DY275E), as per the manufacturer's instructions. The ELISA plates were previously coated with mAb 275 (R+D Systems) at 4 μg/mL. GROα is detected using biotinylated goat anti-human GROα (R+D Systems BAF275) at 200 ng/mL using TMB as a substrate. At the end of the ELISA reactions, plates are read at 450 nm on a microplate reader and compared to a standard calibration curve.

The results of the biochemical and cellular assays are set forth in Table 3 below. For each of the ELISA, SPR and RASF assays, "A" indicates a value of less than 100 nM; "B" a value of between 100 nM and 1 μM; "C" a value between greater than 1 μM and 10 μM; and "D" a value of greater than 10 μM. For the HT-29 assay, "A" indicates a value of less than 1 μM; "B" a value of between 1 μM and 10 μM; "C" a value greater than 10 μM. For every assay, a "*" indicates that some binding or activity was observed, but compound concentration was not taken high enough to calculate an IC50 value. Blank cells indicate that the compound was not tested in that particular assay. Some compounds appear more than once in the Table below because they were tested in more than one run in one or more assays.

TABLE 3

Assay Results for Select Compounds of Formula I

Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
100			*		
101			C		*
101			C		
102			D		
103			D		
104			C		
105			C		*
105			B		
106	B		B	D	C
106			B		
107			B		C
107			B		
108			A		B
108			A		B
109			B		B
110			B		C
111			B		
112			A		B
113			B		C
114			B		
115			B		
116			B		
117			B		
118			B		
119			B		
120			*		B
121			B		
122	C		C	C	
123	*		C	*	
124			B		
125			B		
126			B		
127			B		
128			B		
129			*		
130			*		
131			*		
132			*		
133			*		
134			B		
135			B		
136			A		
137			B		
138			B		
139			B		
140			B		
141			A		B
142			A		B
143	A		A	C	A
144	A		A	C	B
145			A		
146			A		
147			B		
148			B		
149			A		
150			A		
151			A		
152			B		
153	A		A	C	
154			A		
155			A		
156			A		
157			A		
158	A		A		
159	A		A	C	A
159	A		A	C	
159	A				
160			A		
161			A		
162			A		
163			A		
164	A		A		
165			A		
166			A		
167			A		

TABLE 3-continued

Assay Results for Select Compounds of Formula I

Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
168			A	C	
169	B		A	D	
170			A		
171			A		
172			A		
173			A		
174			B		
175			B		
176			B		
177			A		B
178			B		
179		A	B		
180	A		A		A
181	A	A	A	C	A
182			B		
183	C		B		
184			A		B
185	A		A	C	B
185	A		A	C	
186	A	A	A	C	
187	A		A		B
188	C		B		
189			A		
190			B		
191	A		A	C	A
192	A		A	C	
193	B		A	*	
194	A	A	A	B	
195	B	A	B		
196	A		A		
197			B		
198	A		A	C	
199	A		A		
200	B		B		
201	B		A	D	
202	A		A		
203	A		A		
204	B		A		
205	A		A		
206	A		A	C	
207	B		A		
208			A		
209	A		A	C	
210			A		
211	A		A	C	
212	B		B		
213	D		B		
214	A		A	*	
215			A		
216	A		A	C	
217	A		*		
218	A	A	*	A	
219	B		*		
220	B		*		
221	C		B		
222	A		A	*	
223	A		A		
224	C		B		
225	C		B		
226	A	A	A	C	
227	B		A	C	
228	A		A	*	
229	A		*		
230	A		A		
231	*	B	B		
232	C		B		
233	B		A		
234	B				
235	B				
236	A			C	
237	A				
238	C				
239	A				
240	A				
241	B				
242	A			D	
243	*				
244	B	A			
245	C				
246	A	A		D	
247	B				
248	A				
249	A				
250	A				
251	B			C	
252	C				
253	B			C	
254	C			D	
255	C				
256	D				
257	B				
258	C				
259	B	A			
260	A			C	
261	A			C	
262	A				
263	A			C	
264	A	A		B	
265	A				
266	A	A		B	
267			B		
268			A		
269			A		
270	C				
271	C				
272	B				
273	B	A		C	
274	A	A		B	
275	B				
276	C				
277	B				
278	C				
279	A				
280	A				
280	A	A			
281	A				
282	A				
283		B			
284	B				
285	A				
286	B				
288	A	A		A	
289	C				
290	B				
291	C				
292	B	A		B	
292		A		C	
293	B	A		C	
294	A				
295					
296	A				
297	A				
298	A				
299	C				
300	B				
301	C				
302	A	A		B	
303	B				
304	B				
305	A	A		B	
306	B				
307	A				
308	B				
309	B				
310	B	A			
311	B	A			
312	B	A			
313	B	A		*	
314	B	A			
315	C	*			

TABLE 3-continued

Assay Results for Select Compounds of Formula I

Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
316	A	A		B	
317	A				
318	B				
319	B				
320	B				
321	B				
322	B				
323	B				
324	B				
325	A	A			
326	B				
327	A				
328	B				
329	B				
330	B				
331	B				
332	B	A		C	
333	B	A			
334	C	*			
335	B	A			
336	B	A		B	
337	B				
338	B	A		D	
339	A	A		B	
340	A	A		B	
341	A	A		A	
342	B	A		B	
343	B				
344	C	B			
345	B	A			
346	C	A			
347	B	A			
348	C	B			
349	C	A			
350	*	B			
351	B				
352	C			D	
353	B	A		C	
354	B	A			
355	C	A			
356	B	A			
357	B	A			
358	B	A			
359	C	A			
360	B	A			
361	B	A		C	
362	C	B			
363	*	B			
364	B	A			
365	*	A			
366	*	B			
367	A	A		A	
368	B	A		B	
369	A	A		A	
370	B	A			
371	*	C			
372	C	B			
373	A	A			
374	A	A			
375	B	A			
376	B	A			
377	A	B			
378	B	A		B	
379	C	A			
380	A	A		B	
381	B	A			
382	B	A			
383	*	C			
384	B	A			
385					
386		A		C	
387		A		*	
388		A		A	
390		*			
391		A			
392		A			
393		A			
394		A			
395		A			
396		A			
397		A			
398		A		*	
399		A		C	
400		A			
401		A			
402		A			
403		A			
404		A			
405		A		B	
406		A		C	
407		B			
408		A		B	
409		B			
410		B			
411		A			
412		B			
413		A		D	
414					
415		B			
416		A			
417		B		*	
418		A			
420		B		*	
421		C			
422		C			
423		C			
424		A		D	
425		A		B	
425		*			
426		B			
427		A		C	
428		A			
429		A			
430		A			
431		A			
432		A			
433		A			
434		A		B	
435		A			
436		B			
437		B		C	
438		A		B	
439		A		B	
440		B			
441		A		B	
442		A		C	
443		A		B	
444		A			
445		A			
446		A		B	
447		A			
448		B			
449		B			
450		A			
451		A			
452		C			
453		A		B	
454		C			
455		A		A	
456		B			
457		A		C	
458		C			
459		A			
460		A			
461		A			
462		A			
463		A			
464		A			
465		A		*	
466		A			

TABLE 3-continued

Assay Results for Select Compounds of Formula I

Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
467		A			
468		A			
469		A		C	
470		A		B	
471		B			
472		A			
473		A		B	
474		A		B	
475		A		B	
476		A		B	
477		A			
478		A		C	
479		A		A	
480		A		C	
481		B			
482		A			
483		A			
484		A		B	
485		A			
486		A			
487		A		A	
488		A		C	
489		A			
490		A		C	
491		C			
492		B			
493					
494		A		B	
495		A		C	
496		A			
497		A		C	
498		C			
499		A		B	
500		A			
501					
502		A		C	
503		C			
504		B			
505		C			
506		*			
507		A		C	
508		B			
509		B			
510		B			
511		A			
512		A		B	
513		A		B	
514		B			
515		A		A	
516		D			
518		A			
519		A			
520		A			
521		A			
522		A		C	
523		*		*	
523		*			
524		A			
525		A			
526		B			
527		A			
528		A		A	
529		A		A	
530		A			
531		B			
532		B			
533		B			
534		A			
535		A		C	
536		A		B	
537		A			
538		B			
539		A		C	
540		A		C	
541		A			

TABLE 3-continued

Assay Results for Select Compounds of Formula I

Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
542		A			
543		A			
544		A			
545		A			
546		B			
547		B			
548		A			
549		A		A	
550		A		C	
551		A		C	
552		A		A	
553		A		B	
554		A		*	
555		A		A	
556		A		A	
557		B			
558		A		*	
559		A			
560		A		A	
561		A		C	
562		A		C	
563		B			
564		B			
565		A			
566		A		B	
567		A		B	
568		A			
569		A			
570		A			
571		A		C	
572		A			
573		A			
574		A			
575		A			
576		A			
577		A			
578		A			
579		A			
580		A			
581		A			
582		A		C	
583		A			
584		A		C	
585		A			
586		A			
587		A			
588		A			
589		A			
590		A			
591		A			
592		B			
593		A		B	
594		A			
595		A			
596		A			
597		A			
598		*			
599		A			
600		A		C	
601		A		C	
602		A			
603		A			
604		A			
605		A			
606		D			
607		D			
608		D			
609		D			
610		D			
611		A			
612		A			
613		A			
614		A			
615		A			
616		A			

TABLE 3-continued

Assay Results for Select Compounds of Formula I

Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
617		A			
618		A			
619		A			
620		A			
621		A			
622		B			
623		A			
624		D			
625		B			
626		A		B	
627		A		B	
628		A			
629		A			
630		A			
631		A			
632		B			
633		A			
634		A			
635		A			
636		A			
637		A			
638		A			
639		A		C	
640		A			
641		A			
642		A			
643		A			
644		A			
645		A		B	
646		A		C	
647		A			
649		A			
650		A			
651		A			
652		B			
653		A		C	
654		A			
655		A			
656		A		A	
657		A		A	
658		A		A	
659		A			
660		A		A	
661		A		A	
662		A		A	
663		A			
664		A			
665		A			
666		A			
667		A			
668		A			

TABLE 3-continued

Assay Results for Select Compounds of Formula I

Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
669		A			
670		A			
671		A			
672		A			
673		A			
674		A			
675		A			
676		A			
677		B			
678		A			
679		A			
680		B			
681		A			

E. Murine Model of Delayed Hypersensitivity

We used a murine model of fluorodinitrobenzene (DNFB)-induced ear edema to test the anti-inflammatory activity of both orally dosed and intraperitoneally dosed exemplary compounds of the invention. BALB/c mice (Harlan Sprague-Dawley, Inc., male, 6-8 weeks old) were topically treated on their shaved abdomen with 30 μL of 0.5% 1-fluoro-2,4-dinitrobenzene (DNFB) (4:1 acetone:olive oil) once on Day 0 and once on Day 1.

For oral dosing ("PO"), exemplary compounds of the invention were either suspended at 3 mg/mL in 20% Cremophor EL (Sigma) (20:80; Cremophor:water) or dissolved at 1 mg/mL or 3 mg/mL in D-α-tocopherol polyethylene glycol 1000 succinate (TPGS; Sigma)/PEG-400/water (20:60:20). For intraperitoneal dosing ("IP"), exemplary compounds of the invention were dissolved in DMSO at a concentration of 5 mg/mL. On day 7, the test compound was administered (PO at either 10 mg/kg or 30 mg/kg; IP at 1, 3, or 10 mg/kg) to DNFB-treated mice. Commercially available anti-mouse IL-17A (BioLegend) administered intraperitoneally at 5 mg/kg in PBS was used as a positive control. Thirty minutes later, 20 μL of 0.2% DNFB was applied to the right ear of animals and vehicle (DNFB:olive oil) was applied to the left ear. One and four hours after DNFB challenge, a subset of mice was exsanguinated and plasma prepared from the blood. Twenty-four hours after challenge, the remaining mice were euthanized, and their ears were removed and weighed to determine the amount of edema. Plasma was assayed for interleukin-6, TNF-α, CXCL1, and interferon-γ concentrations using commercially-available assays. The results are shown in FIGS. **1-5** and summarized in Table 4, below.

TABLE 4

Delayed Hypersensitivity Assay Results for Select Compounds of Formula I

Cmpd No.	Route	Dose (mg/kg)	IL6 Reduction (%)	IFNγ Reduction (%)	CXCL1 Reduction (%)	TNFα Reduction (%)	Reduction in edema (%)
159	po	10	29.8	24.2			19.0
	po	30	58.3	64.5			53.7
465	po	30	42.5	47.4			23.5
453	po	3	9.3	29.2	−17.0		7.7
	po	10	35.9	35.6	31.0		36.7
	po	30	66.5	67.7	64.3		66.7
474	po	3	6.5	9.3	25.9		9.7
	po	10	22.5	29.5	44.6		23.1
	po	30	70.8	82.9	87.0		67.3
475	po	10	29.7	11.3	61.4		19.2
	po	30	51.9	45.0	63.0		49.5
159*	ip	10		28.5		21.7	54.1
	ip	10	78.6	82.2			54

TABLE 4-continued

Delayed Hypersensitivity Assay Results for Select Compounds of Formula I

Cmpd No.	Route	Dose (mg/kg)	IL6 Reduction (%)	IFNγ Reduction (%)	CXCL1 Reduction (%)	TNFα Reduction (%)	Reduction in edema (%)
	ip	3	72.2	85.5			44
	ip	1	62.6	54.2			17
181	ip	10		38.9		25.5	50.1

*Compound 159 was tested in this assay on two separate occasions.

FIG. **1** demonstrates that Compounds 159 and 181 administered i.p. at 10 mg/kg both produced a statistically significant reduction in TNF-α, IFN-γ and edema as compared to a PBS control or DMSO control. FIG. **2** demonstrates that Compound 159 administered i.p. at 1 mg/kg, 3 mg/kg, or 10 mg/kg, produced a statistically significant reduction in IL-6, IFN-γ and edema compared to a DMSO control. FIG. **3** demonstrates that Compound 453 in a 20% Cremophor Cremophor vehicle demonstrated an effective, dose-dependent decrease in IL-6, IFN-γ, CXCL-1, and edema when administered orally. At oral doses of 30 mg/kg, Compound 453 exhibited edema and biomarker suppression equivalent to anti-IL-17A antibody (anti-mouse IL-17 monoclonal antibody, BioLegend, Inc.) administered at 5 mg/kg (i.p.). FIG. **4** demonstrates that switching to the TPGS-PEG400 oral formulation improved the oral activity of Compound 453 relative to the Cremophor results in FIG. **3**. Compound 453 administered orally at 10 mg/kg in a TPGS/PEG400/Water vehicle decreased IL-6, IFN-γ, CXCL-1, and edema as compared to any of water, 20% Cremophor vehicle alone, or TPGS/PEG400/Water vehicle alone. FIG. **5** shows that orally dosed Compound 159 in TPGS/PEG400/Water vehicle effectively reduced IL-6, IFN-γ, and edema in a dose-dependent manner.

F. Mouse Collagen-Induced Arthritis Model

Exemplary compounds of the invention were evaluated in a murine CIA model. DAB-1 mice (10/group) were anaesthetized with Isoflurane, shaved at the base of the tail, and injected intradermally with 150 μL of Freund's Complete Adjuvant (Sigma) containing bovine type II collagen (Elastin Products, Owensville, Mo.) (2 mg/mL) at the base of the tail on day 0 and again on day 21. On study days 24-25, onset of arthritis occurred and mice were randomized into treatment groups. Randomization into each group was done after swelling was obviously established in at least one paw (score of 1), and attempts were made to ensure approximately equal mean scores of 0.25 across the groups at the time of enrollment. Once a day oral treatment with 10 or 30 mg/kg of test compound in 20% Cremophor EL was initiated after enrollment and continued once a day as indicated through arthritis day 10. Mice were terminated on day 11. Clinical scores were calculated for each of the paws (right front, left front, right rear, and left rear) on arthritis days 1-11 and the results were summarized as a reduction in clinical arthritis score for all paws over the time period of dosing.

As shown in FIG. **6**, Compound 453 administered orally at 30 mg/kg in 20% Cremophor EL reduced mean Clinical Arthritis Score over time as compared to the vehicle control. FIG. **7** shows that this reduction was 11%. FIG. **8**, however, suggests that Compound 453 administered orally at 30 mg/kg in 20% Cremophor EL had little effect on histological parameters. The overall effect on histological parameters was 5% as shown in FIG. **9**. FIG. **10** demonstrates that Compound 159 administered orally at 10 and 30 mg/kg in 20% Cremophor EL demonstrated superior reduction in mean Clinical Arthritis Score on days 27-30 as compared to either TPGS/PEG400 vehicle control or 20% Cremophor EL vehicle control. FIG. **11** shows that Compound 159 reduced the overall mean Clinical Arthritis Score by 6% at 10 mg/kg and 11% at 30 mg/kg.

INCORPORATION BY REFERENCE

The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

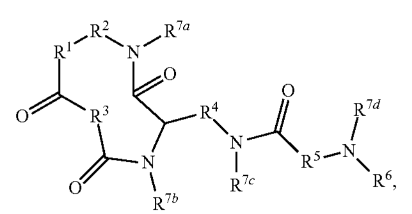
EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A compound represented by Formula I:

(I)



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from —O— and —N((C_0-C_3 alkylene)-Q)-, wherein

Q is selected from hydrogen, —N(R^{7e}), —OH, —O—C_1-C_4 alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

the alkylene portion of R^1, if present, is optionally substituted; and

when the —C(O)— group adjacent to R^1 is bound directly to an —N(R^{7h})— in R^3, R^1 is additionally selected from —CH_2—;

R^2 is an optionally substituted C_3-C_{12} alkylene, optionally substituted C_3-C_{12} alkenylene, or optionally substituted C_3-C_{12} alkynylene, wherein:

up to three methylene units of R^2 are optionally and independently replaced with —O—, —N(R^c)—, —S—, —S(O)—, or —S(O)$_2$—, wherein

R^c is selected from hydrogen, C_1-C_4 alkyl, —C(O)—C_1-C_3 alkyl, —C(O)—(C_1-C_3 alkylene)-aryl, —C(O)—

$(C_1\text{-}C_3$ alkylene)-heteroaryl, —C(O)—O—$C_1\text{-}C_3$ alkyl, —C(O)—O—$C_1\text{-}C_3$ alkenyl, —$S(O)_2$—$C_1\text{-}C_3$ alkyl, —$S(O)_2$—$(C_1\text{-}C_3$ alkylene)-aryl, and —$S(O)_2$—$(C_1\text{-}C_3$ alkylene)-heteroaryl; or

when R^1 is —N(($C_0\text{-}C_3$ alkylene)-Q)-, R^c is optionally taken together with R^1 and any intervening atoms to form a heterocyclyl;

any two substituents bound to a common carbon atom in R^2 are optionally taken together to form ═O, carbocyclyl, or heterocyclyl;

any two substituents bound to different carbon atoms in R^2 are optionally taken together with any intervening atoms to form an aryl, heteroaryl, carbocyclyl, or heterocyclyl;

any two R^c are optionally taken together with the nitrogen atoms to which they are bound and any intervening atoms to form a heterocyclyl; and

any substituent bound to a carbon atom in R^2 is optionally taken together with any one R^c or with R^{7a} and any intervening atoms to form heteroaryl or heterocyclyl;

R^3 is —$[C(R^d)(R^d)]_p$—$[N(R^{7h})]_{0\text{-}1}$—$[C(R^d)(R^d)]_q$—, wherein:

each R^d is independently selected from hydrogen and a suitable alkylene substituent; and any two R^d are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl, or heterocyclyl;

p is 0, 1 or 2;

q is 0, 1 or 2; and

p+q is 2 or more;

R^4 is —$[C(R^e)(R^e)]_n$—Y—$[C(R^e)(R^e)]_m$—, wherein:

each R^e is independently selected from hydrogen and a suitable alkylene substituent;

Y is selected from aryl, heteroaryl, carbocyclyl, heterocyclyl, and optionally substituted $C_1\text{-}C_3$ alkylene;

each of n and m are independently selected from 0, 1, 2, 3, 4, 5, and 6; and

n+m is 6 or less;

R^5 is $C_1\text{-}C_2$ alkylene substituted with one or more —($C_0\text{-}C_5$ alkylene)-R^f, wherein each R^f is independently selected from —CH_3, —O—$C_1\text{-}C_3$ alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R^6 is selected from heteroaryl, —CH_2-aryl, —C(O)—R^8, —C(O)—O—R^8, —C(O)—C(O)—R^8, —S(O)—R^8, —$S(O)_2$—R^8, C(O)—N(R^{7f})—R^8, and —$S(O)_2$—N(R^{7f})—R^8;

each R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} is independently selected from hydrogen and $C_1\text{-}C_4$ alkyl;

R^{7h} is independently selected from hydrogen, $C_1\text{-}C_4$ alkyl, phenyl, and benzyl;

R^8 is selected from —($C_0\text{-}C_6$ alkylene)-aryl, —($C_0\text{-}C_6$ alkylene)-heteroaryl, —($C_0\text{-}C_6$ alkylene)-carbocyclyl, —($C_0\text{-}C_6$ alkylene)-heterocyclyl, and $C_1\text{-}C_6$ alkyl, wherein

when R^8 is $C_1\text{-}C_6$ alkyl, up to two methylene units in the alkyl are optionally and independently replaced with —O—, —N(R^{7g})—, —S—, —S(O)—, or —$S(O)_2$—; and

any alkyl or alkylene portion of R^8 is optionally substituted with an appropriate alkyl or alkylene substituent other than ═O; or

R^{7d} and R^6 are optionally taken together to form a heterocyclyl; and

any aryl, heteroaryl, carbocyclyl, or heterocyclyl portion of the compound is optionally substituted.

2. The compound of claim **1**, wherein R^1 is selected from —O—, —N(H)— and —N(CH_3)—.

3. The compound of claim **1**, wherein R^2 is selected from *—CH(R^{10})—Z— and *—C(H)(R^{10})—X—C(H)(R^{10})—N(R^{12})—C(O)—C(H)(R^{11})—$(CH_2)_{0\text{-}2}$—, wherein:

X is selected from —CH_2—O—CH_2—, —CH_2—N(H)—CH_2—, —CH_2—N(CH_3)—CH_2—, —CH_2—, —$(CH_2)_2$—, and —$(CH_2)_3$—;

Z is selected from $C_2\text{-}C_8$ alkylene, $C_2\text{-}C_8$ alkenylene, or $C_2\text{-}C_8$ alkynylene, wherein up to 2 methylene units in Z are optionally and independently replaced with —O—, —N(H)— or —N(CH_3)—;

each R^{10} is independently selected from hydrogen and —(R)—COOH, wherein at least one R^{10} is hydrogen;

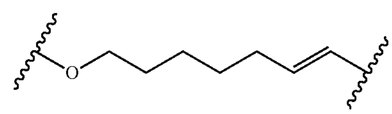
R^{11} is selected from hydrogen, (S)—CH_2OH, (S)—CH_3, (S)—$C(CH_3)_3$, (S)-benzyl, (R)-benzyl, (S)—CH_2-pyridinyl, (S)-cyclohexyl, (S)—CH_2-cyclohexyl, (S)—$(CH_2)_2$—COOH, (S)—$(CH_2)_2$—C(O)NH_2, and (S)—$(CH_2)_4$—NH_2;

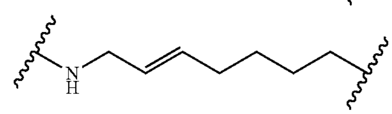
R^{12} is selected from hydrogen and —CH_3; and

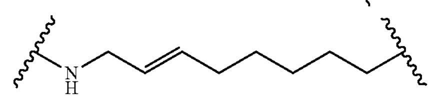
"*" represents a terminus of R^2 bound to R^1.

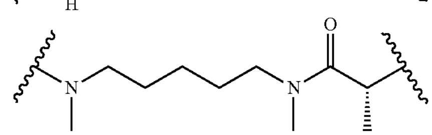
4. The compound of claim **1**, wherein R^2 is selected from *—$(CH_2)_{3\text{-}9}$—, *—CH(COOH)—$(CH_2)_{2\text{-}8}$—, *—$(CH_2)_2$—O—$(CH_2)_2$—, *—$(CH_2)_2$—O—$(CH_2)_2$—O—$(CH_2)_2$—, *—$(CH_2)_2$—NH—$(CH_2)_2$—, *—$(CH_2)_2$—N(CH_3)—$(CH_2)_2$—, *—CH_2—C≡C—$(CH_2)_{4\text{-}5}$, and *—CH_2—CH═CH—$(CH_2)_{4\text{-}5}$.

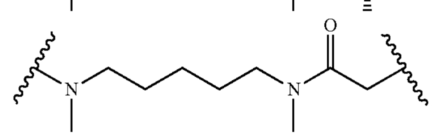
5. The compound of claim **1**, wherein the portion of the compound represented by —R^1-R^2 is selected from:

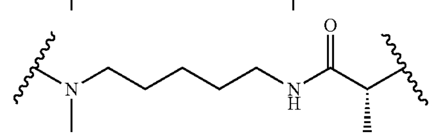

,

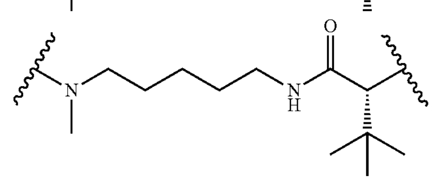

,

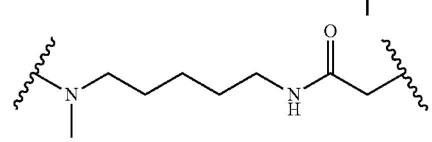

,

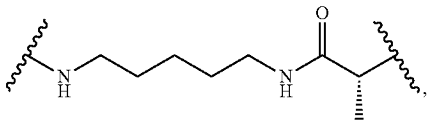

,

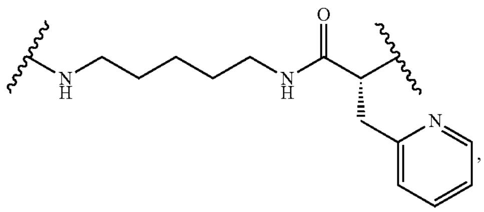

,

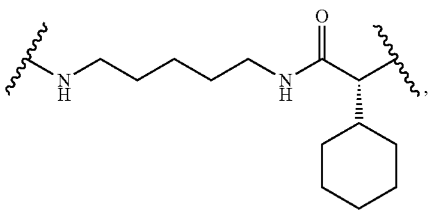

,

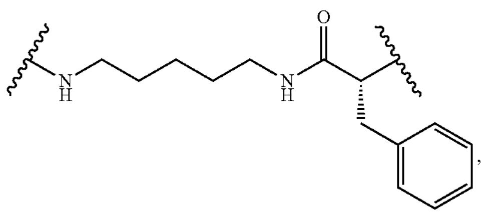

,

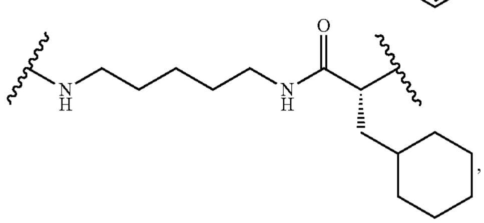

,

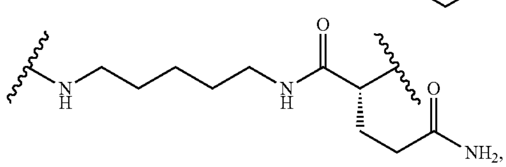


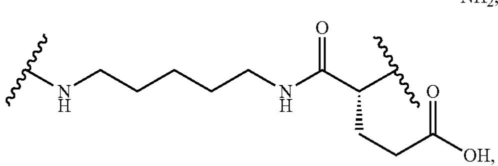


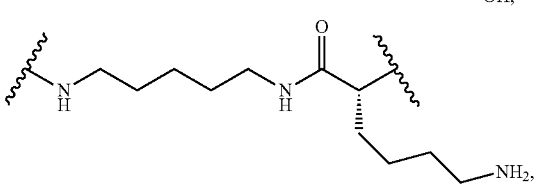


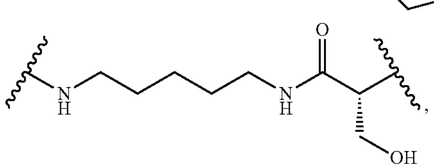


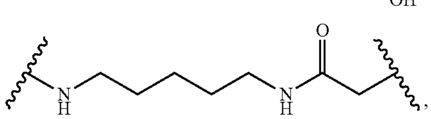


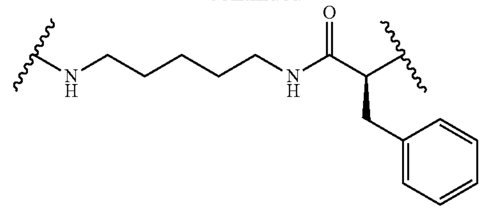


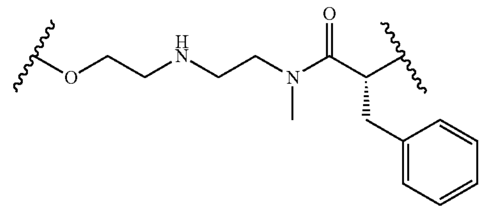


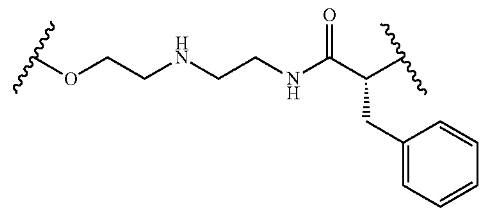


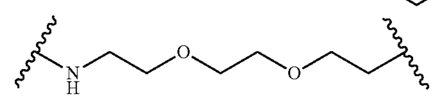


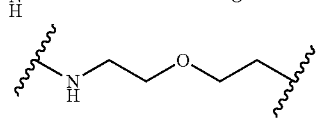


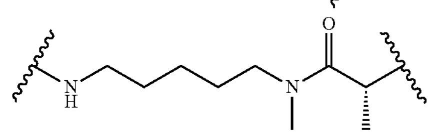


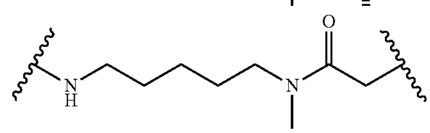


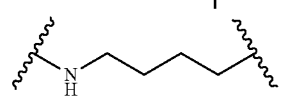


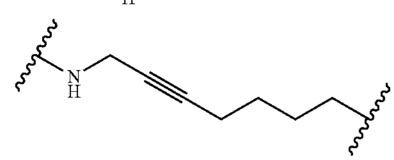


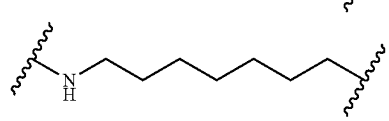


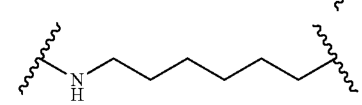


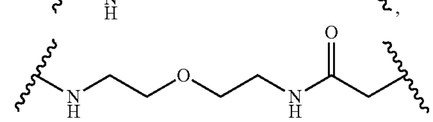


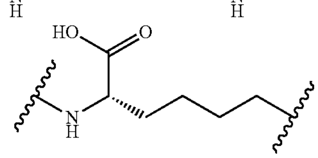




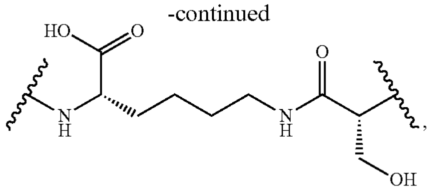


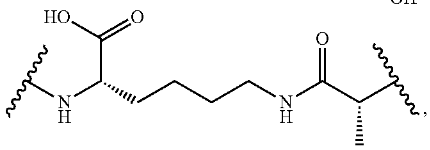


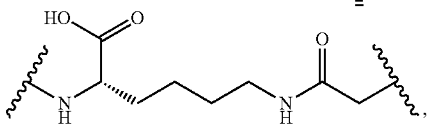


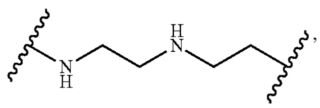


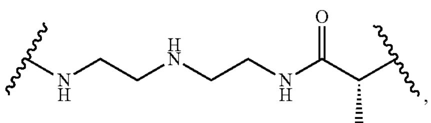
-continued

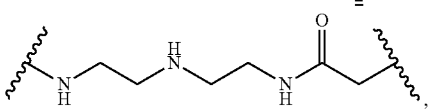


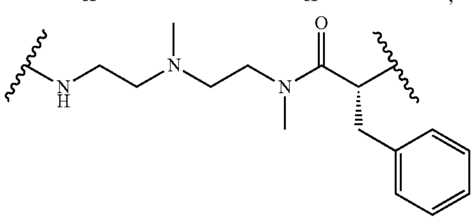


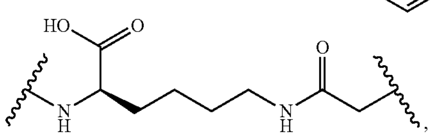


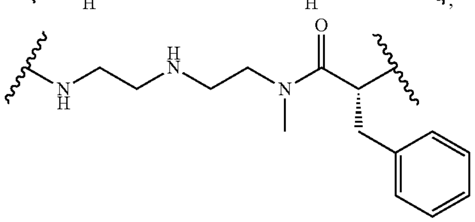


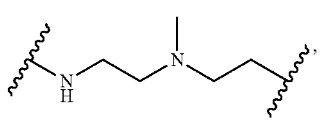


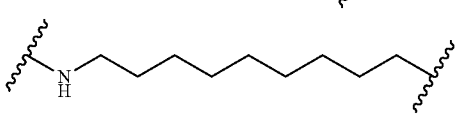


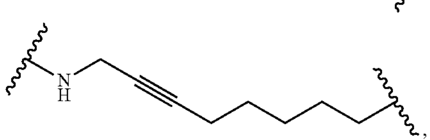


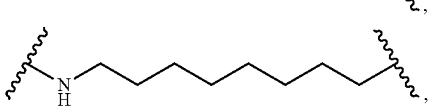




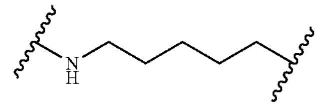


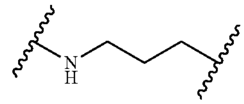


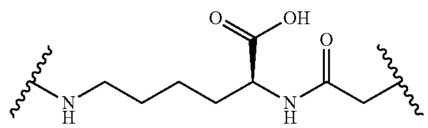


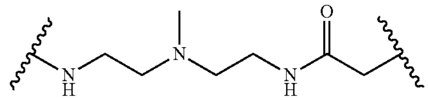


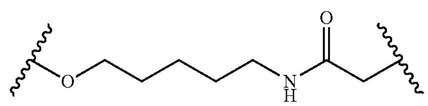
-continued

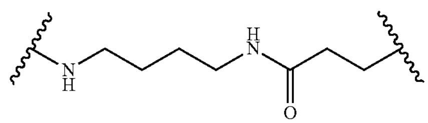


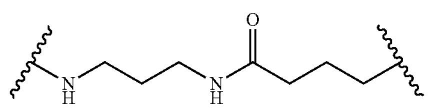


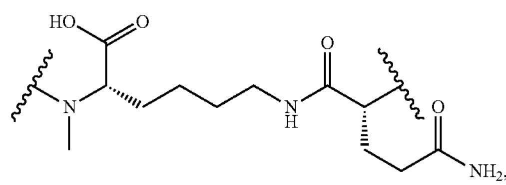


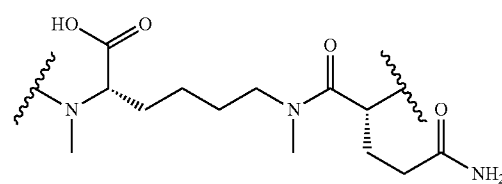


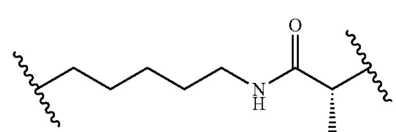


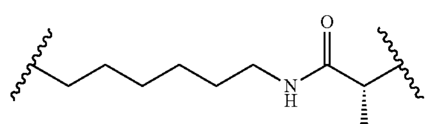


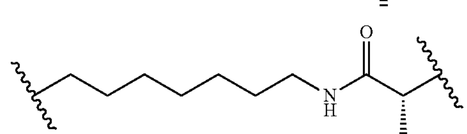


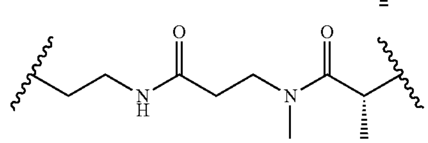




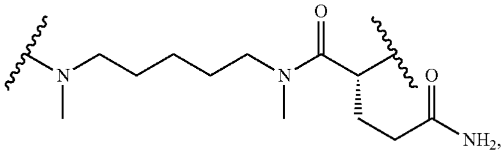


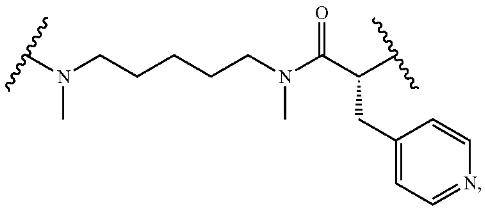


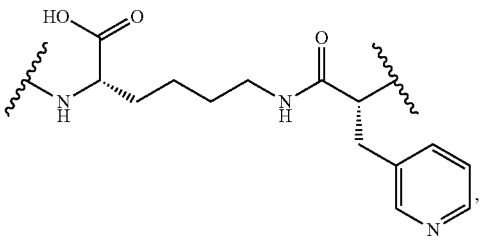


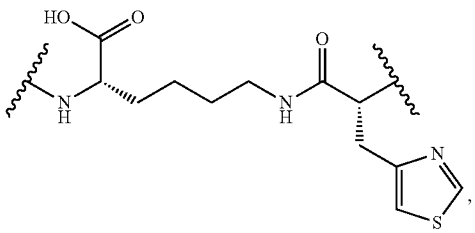


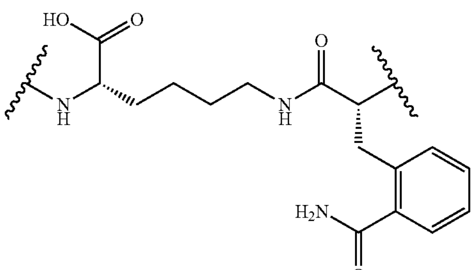
-continued

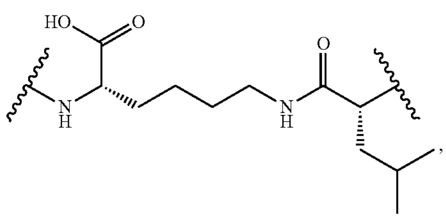


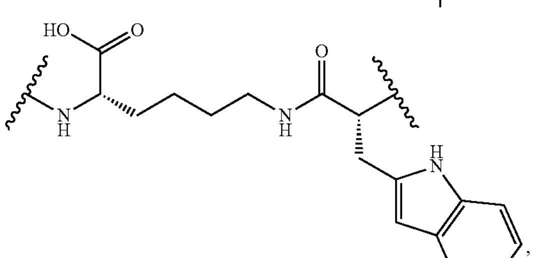




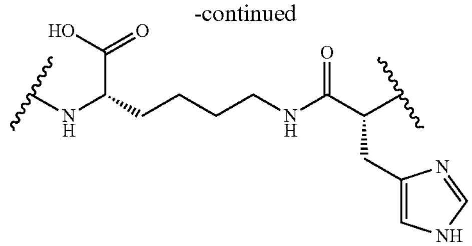


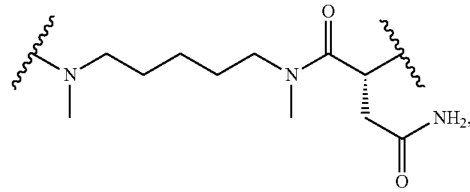


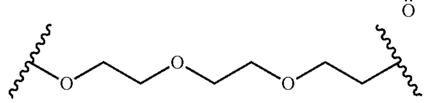




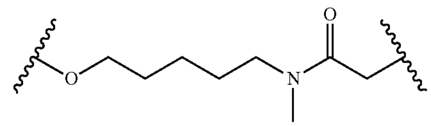
-continued



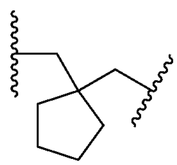


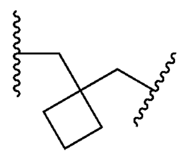


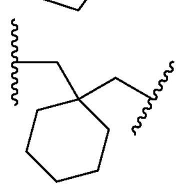
and

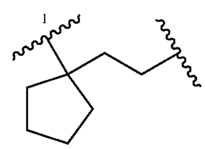


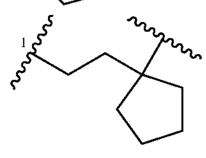
6. The compound of claim **1**, wherein R^3 is selected from —CH_2—$C(CH_3)_2$—CH_2—, —CH_2—$N(CH_3)$—CH_2—,

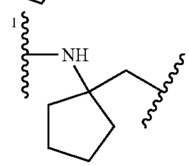


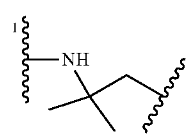


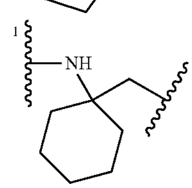


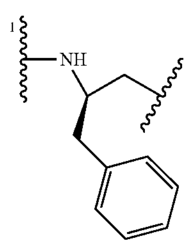




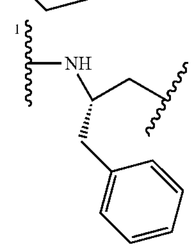








and



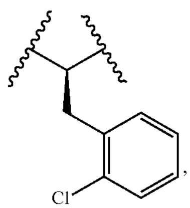
wherein "1" represents a portion of R^3 bound to the carbonyl moiety that is bound to R^1.

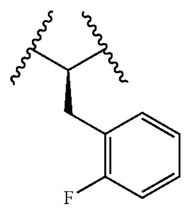
7. The compound of claim **1**, wherein R^4 is selected from —$(CH_2)_4$— and —CH_2-(1,4-phenylene)-†, wherein "†" represents a portion of R^4 bound to $N(R^{7c})$.

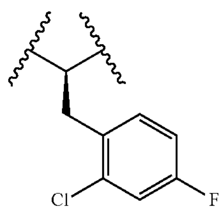
8. The compound of claim **1**, wherein R^4 is —CH_2-(1,4-phenylene)-†; and the stereochemistry of the carbon adjacent to R^4 is (S).

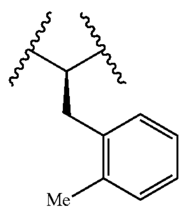
9. The compound of claim **1**, wherein R^5 is —C(H)((R)-benzyl)- wherein a phenyl portion of the benzyl is optionally substituted with up to two substituents independently selected from bromo, chloro, fluoro, methyl, and —CF_3; or R^5 is selected from —C(H)(CH_2—(C_4-C_6 cycloalkyl))-, —C(H)(C_4-C_6 cycloalkyl)-, —C(H)(CH_2-thienyl)-, —C(H)(CH_2-furanyl)-, —C(H)(heterocyclyl)-, —C(H)(CH(CH_3)-(aryl))-, —C(H)(CH(CH_3)-(heteroaryl))-, —C(H)(CH(CH_3)-(heterocyclyl))-, —C(H)(CH(CH_3)-(carbocyclyl))-, and —C(H)(C_3-C_4 alkyl)-.

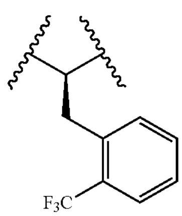
10. The compound of claim **1**, wherein R^5 is selected from:

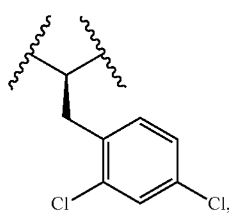
,

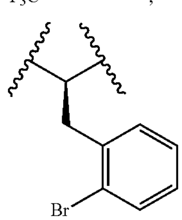
,

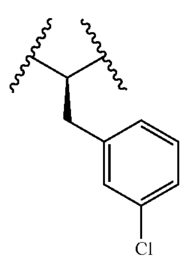
,

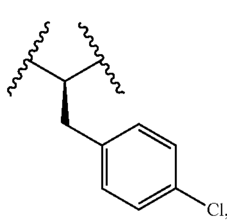
,

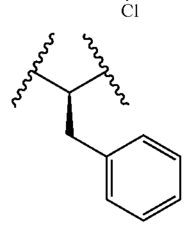
,



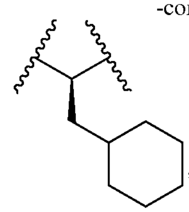
,

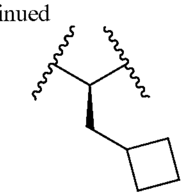
,

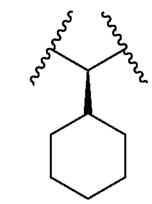


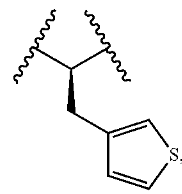
,

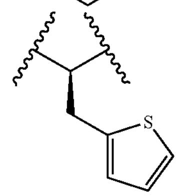
-continued

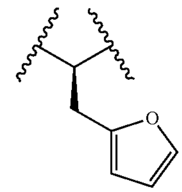
,

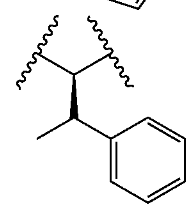
,

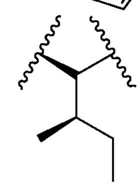
,

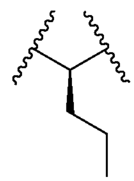


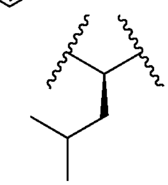
,

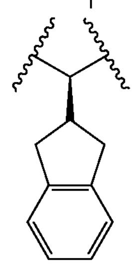
,

,

,

,

, and

.

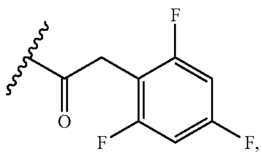
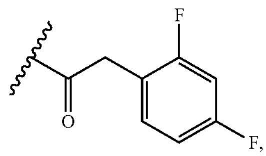
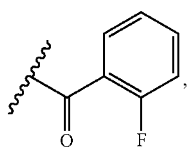
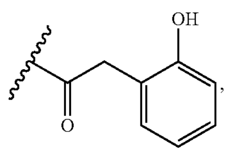
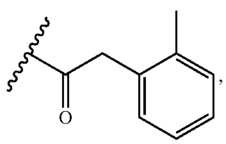
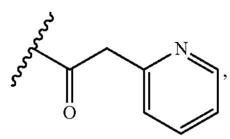
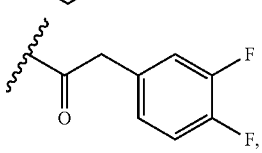
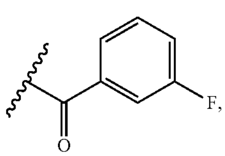
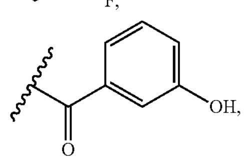
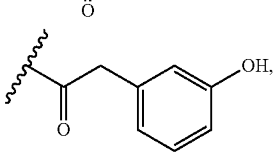
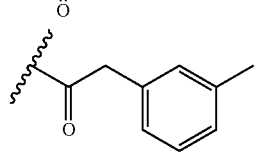
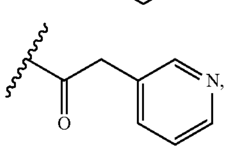
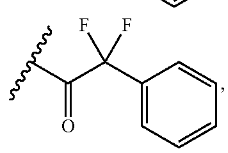
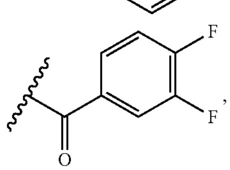
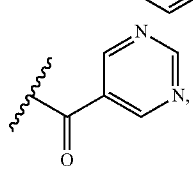
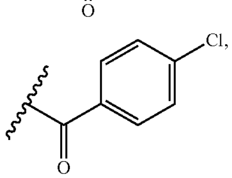
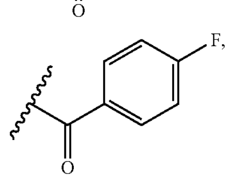
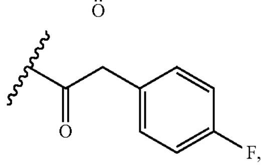
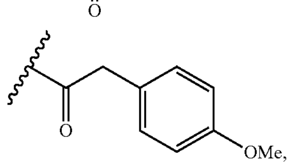
11. The compound of claim **1**, wherein R^6 is —C(O)—$[C(R^{13})_2]_{0-1}$—R^{9a}; wherein R^{9a} is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, C_1-C_4 alkyl, —O—C_1-C_4 alkyl, —N(H)—CH_3, —$N(CH_3)_2$, and —N(H)—CH_2-aryl, wherein R^{9a} is optionally substituted with up to 2 substituents independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, C_1-C_4 alkoxy, —O—$(CH_2)_2$-morpholin-4-yl, —O—$(CH_2)_2$—$N(R^{14})$—CH_2-phenyl, —N(H)—C(O)—CH_2—N(H)—CH_2-phenyl, and —O—$(CH_2)_2$—$N(R^{14})_2$; each R^{13} is independently hydrogen or fluoro, or two R^{13} are taken together to form a C_3-C_6 cycloalkyl or ═O; and each R^{14} is independently hydrogen or —CH_3.

12. The compound of claim **11**, wherein R^{9a} is selected from phenyl, pyridyl, quinolinyl, isoquinolinyl, cyclohexyl, 3,3-difluorocyclopropyl, —CH_3, —$C(CH_3)_3$, —OCH_3, —$N(CH_3)_2$, —$N(H)(CH_3)$, and —N(H)-benzyl, wherein R^{9a} is optionally substituted with up to 2 substituents independently selected from fluoro, chloro, methyl, methoxy,

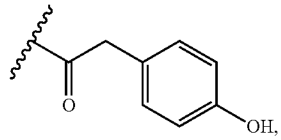
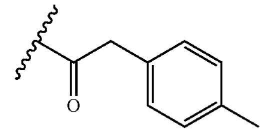
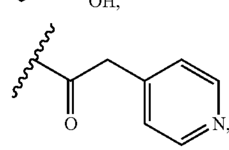
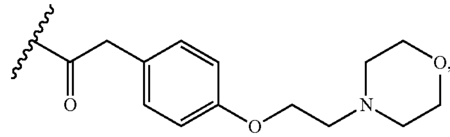
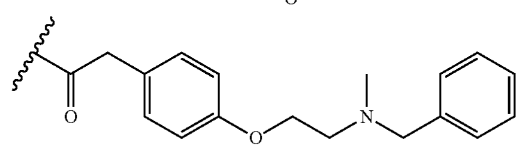
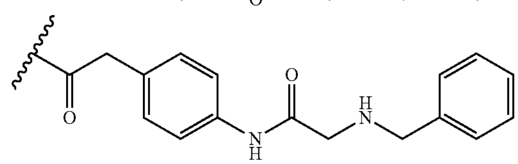
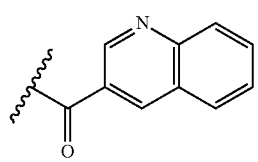
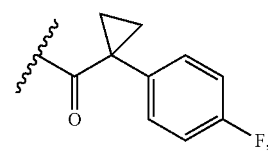
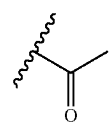
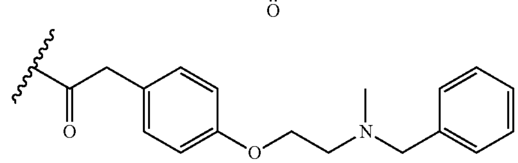
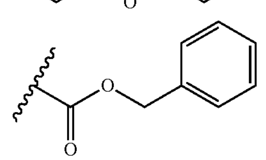
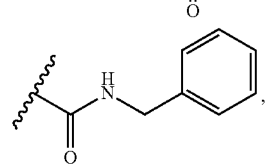
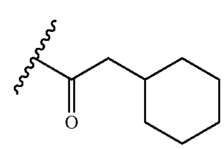
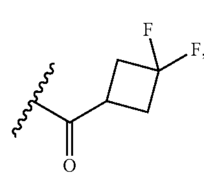
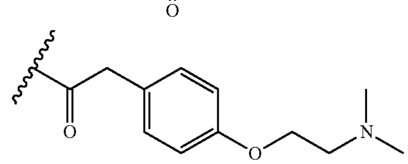
hydroxy, —O—$(CH_2)_2$-morpholin-4-yl, —O—$(CH_2)_2$—N (CH_3)—CH_2-phenyl, and —O—$(CH_2)_2$—$N(CH_3)_2$.

13. The compound of claim **1**, wherein R^6 is —C(O)-benzyl or —C(O)— phenyl, wherein said benzyl and phenyl in R^6 are each optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, C_1-C_4 alkoxyl, and C_1-C_4 alkyl.

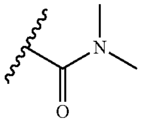
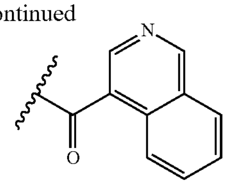
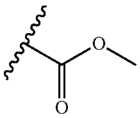
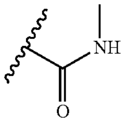
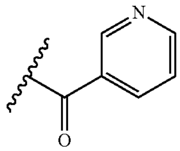
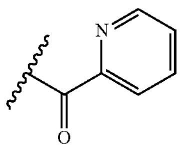
14. The compound of claim **1**, wherein R^6 is selected from:

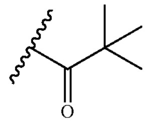
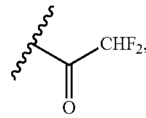
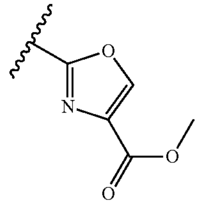
-continued

-continued

,
,
,
,
,
,

-continued

,
, and
.

15. The compound of claim **1**, wherein R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are independently selected from methyl and hydrogen.

16. A pharmaceutical composition comprising a compound of claim **1**, and a pharmaceutically acceptable carrier.

* * * * *